Least Burden and Cost Benefit Analysis
Newborn Screening for Metabolic Disorders
WAC 246-650

August 12, 2003

The Department of Health has made the preliminary determination that the probable benefits exceed the probable costs for newborn screening for the following disorders and equipment combinations:

- Galactosemia using traditional technology at the DOH lab
- Biotinidase deficiency using traditional technology at the DOH lab
- MCADDusing new MS/MS[1]
- Homocystinuria using existing MS/MS
- MSUD using existing MS/MS

Background on Washington's program and rule adoption.

One in 3,000 newborn children carries a metabolic disorder that interferes with the growing child's ability to thrive and live a normal life. Some of these disorders are both detectable and treatable. If screening can detect the disorder early and early treatment makes a difference in the medical outcomes for the children then it is possible that a screening program that covers all infants in the state will have net benefits.

The current rule requires that newborns be screened for 4 disorders: phenylketonuria, congenital hypothyroidism, hemoglobinopathies, and congenital adrenal hyperplasia.

This proposed rule amendment will add the following disorders:

- Biotinidase Deficiency
- Galactosemia
- MCADD (Medium Chain Acyl Co-A Dehydrogenase Deficiency)
- Homocystinuria
- MSUD (Maple Syrup Urine Disease)

The following criteria were used to determine whether it would be beneficial to use screening:

- Prevention Potential and Medical Rationale: Identification of the condition provides a clear benefit to the infant, preventing delay in diagnosis, developmental impairment, serious illness, or death
- Treatment Available: Appropriate and effective screening, diagnosis, treatment and systems are available for evaluation and care

[1] Tandem Mass Spectrometry

- Public Health Rationale: Nature of the condition (symptoms are usually absent, such that diagnosis is delayed and treatment effectiveness is compromised) and prevalence of the condition justify population based screening rather than risk based screening
- Available Technology: Sensitive, specific and timely tests are available that can be adapted to mass screening
- Cost/Benefit Analysis and Cost Effectiveness: The benefits justify the costs of screening

The first four criteria above were applied first based on available data. However, cost benefit analysis is expensive and time consuming. Therefore cost benefit analysis was only done if all the other criteria had already been met. This made sense in that if one of the criteria were not met, the cost benefit analysis would be likely to predict negative net benefits.

This cost benefit analysis evaluates each disorder based on current scientific and technological information. The analysis depends on the type of technology that will be used to detect disorders.

- **Traditional Technology**: Galactosemia, biotinidase deficiency, homocystinuria, and MSUD can be detected with traditional technology that is similar to that currently used by the State of Washington, Department of Health's Public Health Laboratories. However, using traditional technology, Homocystinuria tests miss many of the neonates who have the non-responsive form of the disorder.

- **Tandem Mass Spectrometer Technology**: This analysis shows a different resulting net benefit depending on obtaining MS/MS equipment. MCAD deficiency screening requires this new equipment. This analysis recommends obtaining Tandem Mass Spectrometry (MS/MS) capability. Further, for relatively low marginal cost, MS/MS would be able detect to both responsive and non-responsive Homocystinuria infants, and MSUD infants. Screening for Homocystinuria and MSUD would provide net benefits if the machinery were already purchased for MCADD screening, but not for Homocystinuria and MSUD alone.

Newborn screening blood spots are typically collected on the first and 10^{th} day of life. The results of the screen are available within 7 days.[2] The best time for screening varies based on the disorder. MCADD is most easily diagnosed if the blood spot is taken in the first days after birth while the body has reduced sugar levels. Galactosemia is best diagnosed some time after the first feeding of lactose.

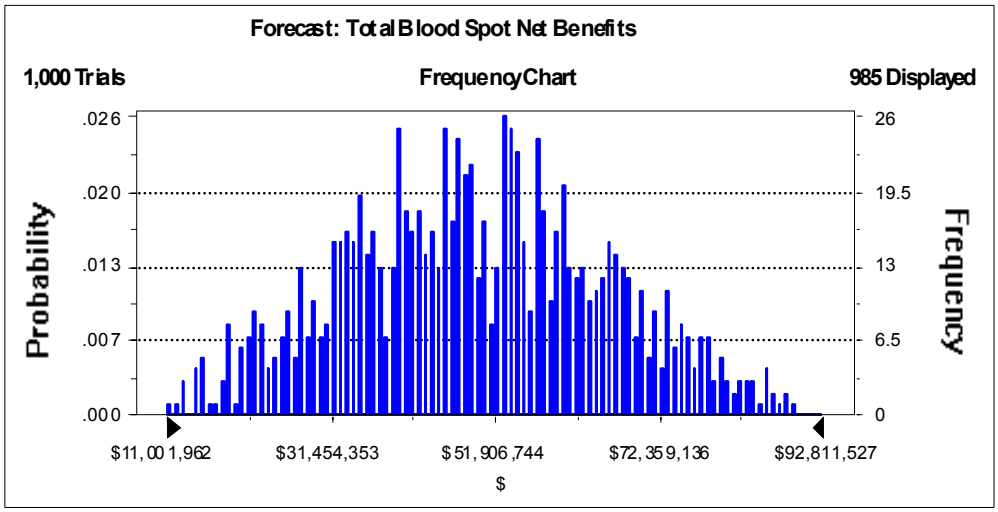
The urgency of rapid detection varies based on the disorder. For Homocystinuria, galactosemia, and MSUD the results of the first blood spot screen become available just as symptoms are developing. Screening would reduce permanent damage by cutting short the duration of exposure to the metabolic disorder. Biotinidase deficiency damages the child more slowly, and without screening, it may take a long time to diagnose. The screen would prevent slower, long-term damage and multiple tests to determine the problem. For MCADD the screen will prevent damage or death in the child when illness or other stressors cause the child to metabolize fats.

[2] Mike Glass, DOH. Bloodspots are generally sent within 24 hours and received within 2 days. The lab processes them within 24 hours of receiving them and notifies the pediatrician if there is a problem. If the pediatrician is not available, the parents are notified. Generally testing and notification occurs in 4 to 7 days.

Ten Year Estimates for Newborn Screening						
	Blood Spot	Traditional Technology		Tandem Mass Spectrometry		
	Totals	Galactosemia	Biotinidase	MCAD	HCY	MSUD
Number of Children	68.0	13.8	10.3	30.8	4.9	8.3
Mortality Shift	-15.6	-4.4	-2.8	-7.1	-0.2	-1.0
Reduced cost of clinical Identification	$ 681,946	$ 145,457	$ 24,353	$ 328,599	$ 45,925	$ 137,611
Mortality avoided	$ 61,144,516	$ 17,178,988	$11,389,861	$ 28,057,737	$ 505,169	$ 4,012,762
Reduced Cost/Cost of Related Disabilities	$ 6,372,544	$ (914,160)	$ 539,301	$ 4,235,084	$ 1,664,430	$ 847,890
Added Food or Medication Costs Due to Mortality Shift	$ 423,846	$ 289,522	$ 10,335		$ 13,239	$ 110,750
Added Medical Intervention & Monitoring Costs	$ 1,013,168	$ 13,204	$ 1,562	$ 947,917	$ 5,707	$ 44,779
Added Clinical and Monitoring Costs Due to Mortality Shift	$ 1,197,286	$				1,197,286
Added Screening Program Costs	$ 14,915,534	$				14,915,534
Net Benefits	$ 50,649,171	$ 13,550,413	$ 9,612,865	$ 22,730,708	$ 1,327,548	$ 3,427,637
$/Year of Life Saved	$ 35,843	$ 27,934	$ 27,442	$ 48,168	$ 45,323	$ 19,840

This cost benefit analysis reviews the shift in medical outcomes with and without newborn screening and the costs created by the screening. Screening creates benefits when negative medical outcomes are reduced or eliminated. However, screening is costly and may create additional costs in the event of false positives.

DOH has used a Monte Carlo procedure to test the sensitivity of most major variables of the newborn screening models. Expected net present value of benefits for a 10 year period for the five metabolic disorders taken together is $50 million with a range from $11 million to $150 million.[3] For the metabolic screening, the expected cost per year of life saved is $36,000. The model is very sensitive to the value of life, which generates over 90% of the variance in the model (see galactosemia discussion page 9).



[3] The range was estimated using a Monte Carlo that allowed significant multipliers to vary based on assigned distributions. The Monte Carlo is a probabilistic means of testing the sensitivity of a model.

Least Burdensome Analysis

The proposed rule is the least burdensome form of the rule. Alternatives examined but rejected including expanding the newborn screening requirements to include tests for the following:

- G6PD. This disorder failed to pass all four of the initial criteria outlined above. In particular, evidence of the prevention potential and medical rationale was judged insufficient.

- Toxoplasmosis. This disorder failed to pass all four of the initial criteria outlined above. In particular, evidence for the efficacy of treatment was judged insufficient.

- Cystic Fibrosis. This disorder had a mixed reading on the first four criteria and uncertain benefits. The Newborn Screening Committee asked the State Board of Health to reconsider Cystic Fibrosis as soon as new data is available.

As for the tests that are required by this rule, the testing is accomplished in the least burdensome manner. Hospitals must already collect blood spots and submit them to DOH, so there are minimal additional costs for hospitals. And the rule gives DOH flexibility to test for the specified disorders in the least costly manner.

Cost Benefit Analysis for Galactosemia

Background

Galactosemia is rare. Its frequency depends on the racial mix of the population. Washington expects one in 60,000 infants (0.0017%) to be born with galactosemia. For Washington this means an average of 13.8 infants will be born with galactosemia in a ten year period.

Galactosemia is a serious metabolic disorder caused by the inability of the body to process galactose into glucose.[4] This results in medical outcomes such as poor weight gain, vomiting, diarrhea, lethargy, hypotonia, jaundice, hepatomegaly, bleeding, anemia, septicemia, IQ deterioration, speech problems, cataracts, seizures, and mortality.

In most infants lactose is broken down into galactose and glucose in the intestine. Once galactose is absorbed, it is then converted to glucose primarily by 3 enzymes of the Lelior pathway:[5] galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and uridine diphosphate galactose-4'-epimerase (GALE). In galactosemic infants one or more of these enzymes are not available in sufficient quantities and galactose or galactose-1-P can build up to toxic levels in the body.

Removing lactose from the diet significantly reduces the galactose level in the diet.[6] Infants who are ill with a variety of symptoms are switched to a soy-based formula to allow the body to recover. The removal may generate an improved IQ outcome for some children. However, the long-term success of the diet depends on the genetic basis of the galactosemia.

Benefits of Galactosemia Screening

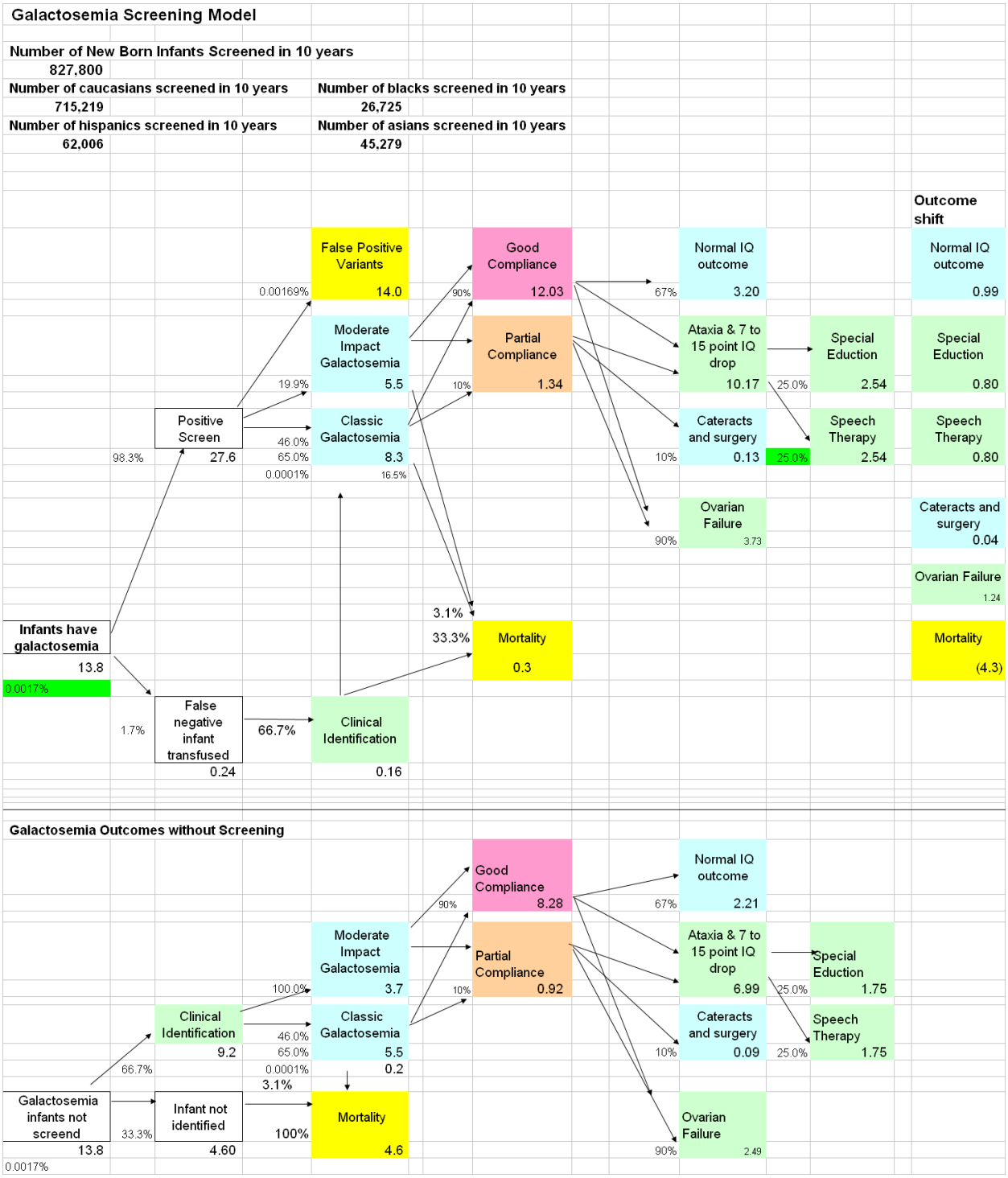
Screening would provide diagnosis just as the infant first presents with symptoms. Screening would allow an immediate shift away from lactose in the diet. Screening and an early diet shift would reduce mortality and the immediate impact of high doses of galactose.

- Some infants will not die. Currently in a 10 year period, a statistical mortality of 4.6 children would be expected from the onset of infections, poor weight gain, vomiting, diarrhea, lethargy, hypotonia, jaundice, hepatomegaly, bleeding, anemia, septicemia, and seizures. With newborn screening the statistical mortality is reduced to .3 children.
- Some infants will avoid brain damage from the early high doses of lactose. All infants with earlier diagnosis would have significantly reduced damage from the early exposure. 1 child would shift from having IQ damage to have a normal IQ outcome with no ataxia.

[4] Much of the overview information on the function of galactosemia is drawn from J. B. Holton, J. H. Walter, and L. A. Tyfield, *Galactosemia*, Chapter 72, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill.

[5] There are other ways that the body transforms galactose such as the pyrophosphorylase pathway or oxidation to galacotanate but these are less effective than the Lelior pathway.

[6] Traces of galactose are found in some fruits and vegetables and the body may generate galactose on its own, however milk and milk products are the primary source.



- Screening is expected to reduce the cost of clinical identification: Currently most Galactosemic infants are hospitalized in neonatal intensive care units with an expected reduced cost of stay of $12,000 per child.
- Finally, screening will identify some infants with Duarte or other forms of mild galactosemia who may benefit from elimination of lactose from the diet. These infants are not counted in the analysis.

Costs of Galactosemia Screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs and negative medical outcomes for children who would otherwise have died:

- Screening all newborns: The DOH expects to screen 827,000 newborns at a cost of $3.15 each. The expected present value of this cost for a 10 year program is $2.3 million.[7]
- Monitoring tests: Children with galactosemia have to be monitored. A child would be expected to have a present value of $4,000 in testing costs.[8]
- Clinical program: The children who would have died would be expected to need the clinical program that currently trains families how to select food, explains test results, and intervenes with the child when he or she decides to eat inappropriately at a cost of $263,000.[9] Diagnostic testing on children who screen positive costs $800 each.
- Food sorting: This is a time consuming activity that involves avoidance of foods that contain lactose. Label reading requires knowing the names of the foods and food additives that contain lactose. This is expected to require 7 hours per month valued at $25 per hour for a total cost of $272,000 over the life span of the children, who would have died.[10]

Long-term medical outcome costs dominate the losses associated with the program. Galactosemia is generated by several genetic defects. Some infants who have classic galactosemia will continue through diet and body generated galactose to decline slowly and will have negative medical outcomes and reduced capacities.

- IQ loss: Some children will experience a long-term deterioration of IQ and may also have speech difficulty and/or ataxia. These are valued based on an IQ loss of between 7 and 15 points. Currently, with average diagnosis periods, 7 children would be expected to experience ataxia, speech problems, and/or a drop in IQ. With screening 10 children would be expected to experience ataxia, speech problems, and/or a drop in IQ. DOH expects 3 additional children will experience IQ loss and half of these will require either speech therapy or special education.[11]
- Cataracts: Some children who do not die will experience development of cataracts and will require surgery.
- Ovarian Failure: 90% of the surviving girls experience a long-term deterioration and finally, ovarian failure. These young women will require replacement hormones and will be unable to bear children.

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[7] Based on a 3% discount rate. The $3.15 per screen is attached to a flat distribution that ranges from $3.00 to $3.30 for the Monte Carlo.

[8] Present value based on 2 blood tests per year for life, at a cost of approximately $300 per year, discounted at a 3% rate.

[9] Based on current average costs for work with 16 children at the clinical program for Metabolic Disorders at the University of Washington and the estimated share of costs based on the disorder.

[10] Based on Tacoma/Seattle average hourly earnings of $18.90 per hour and approximately 30% benefits. Costs are not ascribed to children who would have lived without the screening because there is no change in cost for them.

[11] This may be a very high figure in that all of the classic galactosemic children are expected to have a downward IQ drift and only 67% of the moderate form children with good compliance are forecast to experience no IQ damage. Tentative new evidence, through ten years of screening in Georgia, indicates 1 galactosemic child was missed and developed mental retardation, but 47 children would have been expected to have developed retardation due to galactosemia. The results have been left without adjustment due to earlier literature indicating classic galactosemia yields IQ reductions over time. Given the time frame, some of the cases may not have had a chance to develop and be diagnosed. *Mental Retardation Following Diagnosis of a Metabolic Disorder in Children Aged 3-10 Years*, MMWR, CDC, May 7, 1999, No. 17.

The Galactosemia Medical Outcomes Model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the "front end" or left hand side of the model see Figure). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency**: 1 in 60,000 is the estimated frequency of galactosemia. For purposes of the Monte Carlo, this frequency was attached to a normal distribution ranging from .0011% to .0023%.
- **False Negatives**: DOH expects that 1.7% of the galactosemia cases will be missed by screening due to one of the following reasons: 1. in Washington the failure rate for adequate first blood spots is 1.7%,[12] 2. the infant may have been transfused, or 3. the first blood spot may be taken before the infant is fed lactose.[13]
- **True Positives**: This is a function of 1 minus the rate for false negatives.
- **False Positives**: 1 in 59,000 is the estimated number of false positives.[14]
- **Share of Classic Galactosemics**: Classic galactosemia generates less desirable long-term medical outcomes including IQ and speech deterioration over time. It is caused by several mutations. In North American Caucasians Q188R mutation, which causes classic symptoms, accounts for 60 to 70% of the mutations. Within the galactosemic population DOH has extrapolated the rate of 63.5% to the white population in Washington. In Hispanics of Mexican origin it accounts for 50 – 58%. Given the relative rates of Hispanics of Mexican vs. other Hispanic origins, the DOH has extrapolated the rate of 46% for Washington Hispanics. In Japan, only 1 in a million children is expected to be born with galactosemia. This rate is applied to the Asian population as whole. In the black population, the rates for classic galactosemia range from 12% to 21% of the population. DOH has applied the rate of 16.5% to Washington's black population.[15]
- **Share of moderate impact galactosemics**: Infants with more moderate forms of galactosemia are the remaining portion of the galactosemic population.
- **Mortality** is estimated at 1/3 for the children who are clinically diagnosed, based on recent experience at the University of Washington. Children who have been screened are diagnosed more rapidly because the results become available just as the child is presenting with symptoms. The estimated mortality for true positive screened infants is 3.1%.
- **Diet Compliance**: Parents and children who comply with dietary restrictions have better outcomes. Generally compliance is excellent because the immediate physical consequences include vomiting, illness and possibly shock and hospitalization. However, 10% partial compliance was assumed in order to provide a conservative analysis.
- **IQ outcomes**: 2 out of 3 of the moderate impact children with good compliance are expected to have normal IQ outcomes. The remaining 1/3 of the children and all the

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[12] Based on the square root of the overall failure rate of 1 in 3000 for the two blood spots taken together. Mike Glass, DOH.

[13] In Georgia 1 in 47 cases was missed. This would yield an estimate of 2.1%. *Mental Retardation Following Diagnosis of a Metabolic Disorder in Children Aged 3-10 Years*, MMWR, CDC, May 7, 1999, No. 17. This information was used to set the mean for a Weibull distribution in the Monte Carlo.

[14] The Magnitude and Challenge of False Positive Newborn Screening Test Results, Charles Kwon, Phillip Farrell, Archives of Pediatric Adolescent Medicine, vol. 154, July 2000

[15] *Galactosemia*, Chapter 72, J. B. Holton, J. H. Walter, and L. A. Tyfield, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill, pages 1564 through 1567.

children with partial compliance are expected to have some IQ loss.[16] The loss, without screening, is expected to be more moderate than with screening but the shift is difficult to quantify. Treatment has improved and diagnosis may now be more rapid even without screening. Based on earlier paired sibling data the average period of identification for the index sibling (the first child in the pair) was 23.5 days for Waggoner's data and 64 days for Fishler's data.[17] However, several physicians on the Newborn Screening Committee[18] felt that most pediatricians would identify galactosemia more quickly than this. Given a maximum of 7 days turn-around for the screen and the old data, this could save the average infant from 16.5 days of exposure to toxic levels of galactose. Further, the IQ impact is DNA dependent. In order to be conservative about the benefits of screening, DOH has assumed that the range of long-term IQ reduction is similar with and without screening. This means that, the full cost of any potential IQ losses experienced by the surviving children are ascribed to the program.

- **Special education or speech therapy**: Of those experiencing IQ loss or ataxia, 25% are expected to need special education and 25% are expected to need speech therapy.[19]
- **Cataracts**: Approximately 10% of the children will have cataracts, which require surgery. For children with GALT or GALK deficiency, changes may occur that are not reversible if lactose is not removed from the diet early in their infancy. For some Galactosemics, with GALK deficiency, cataracts are an indicator that may lead to diagnosis when no screening is available.
- **Ovarian Failure**: 90% of the girls with galactosemia will develop ovarian failure and require hormone replacement therapy. They will be unable to have children.

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo procedure, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is large and values range from $1 to $16 million.[20] The values are based on cost of illness, wage and risk studies, and reported willingness to pay. The values cluster in the $3 million to $7 million range. DOH has chosen $4 million dollars as the value of life. This value has been assigned a Weibull distribution with a range from $1 million to $7 million in value for the Monte Carlo.
- Minor **neural damage that reduces IQ** reduces the function of the individual in all areas of life. Without retardation, loss of IQ generates a loss of productivity that is valued at

[16] C. Ronald Scott, M.D., Professor, Pediatrics & Medicine, University of Washington School of Medicine

[17] Raw data were taken from Galactosemia: New Frontiers in Research, ed. George M Donnell, National Institutes of Health, National Institute of Child Health and Human Development, "Long Term Prognosis in Galactosemia: Results of a Survey of 350 Cases," Diane Waggoner, and data from "Intellectual Development in Galactosemia," Karol Fishler. Diane Waggoner provided her data directly.

[18] Ron Scott, Ian Glass, Andrew Brunskill, Scott Lindquist.

[19] Verbal dyspraxia is reported at rates of 57% for children with 20th percentile cranial size and up. The Washington experience is better than this (25%) but there is a small numbers problem and these numbers should be used with caution. For the Monte Carlo the estimate was attached to a uniform distribution ranging from .25 up to .57.

[20] For a discussion of the literature see: Cost Benefit Analysis, Richard Layard and Stephen Glaister, Cambridge University Press, 1994; and W. Kip Viscusi "The Value of Risks to Life and Health" J. of Econ. Lit. Vol 31 Dec. 1993, a survey of the literature. Viscusi is also in: Journal of Risk and Uncertainty Vol 8 No 1 1994 reprinted by Kluwer Academic Publishers which has a large set of articles with arguments on values from both sides.

$14,500 per IQ point, in 2000 dollars, with a range from $12,700 to $17,200.[21] Thus even when the difference in IQ is as small as a few IQ points, a loss is imposed on the individual. This value has been assigned a Weibull distribution with values ranging from $12,700 to $17,000 for the Monte Carlo.

- **Cateract surgery** costs are estimated at $3,500.
- **Ovarian failure** will require hormone replacement therapy at $360 per year and will mean the girl is unable to bear children. This latter is valued at $21,000 per year.[22]

[21] Grosse SD, Matte TD, Schwartz J, Jackson RJ, "Economic gains resulting from the reduction in children's exposure to lead in the United States," Environmental Health Perspectives. 2002. 110(6), in press.

[22] The ability to reproduce is highly valued by some and regarded as a nuisance by others. Couples may spend hundreds of thousands of dollars to conceive a child, where others may opt for tubal ligations. This model uses $21,000 per year which is a lifetime present value of $321,000 using a 3% interest rate and valuing it for the years from 13 through 45 when fecundity would normally occur. This may be a high value, however, if so, it makes the model more conservative.

Net Present Value of Galactosemia Screening Benefits

The addition of galactosemia screening in Washington is expected to generate net benefits of $13.5 million over a period of 10 years. The Monte Carlo procedure indicates a range of $2 million to $28 million, with a mean of $13 million and a standard deviation of $4.6 million.[23]

Estimating Net Benefits		
Gain		**Expected Value**
Mortality avoided	(4.2947)	$ 17,178,988
Reduced cost of clinical Identification	13.8	$ 145,457
Cost		
Mild IQ Loss	1.59	$ (253,750)
Mild IQ Loss and Special Eduction	0.80	$ (80,739)
Mild IQ Loss and Speech Therapy	0.80	$ (173,011)
Cateracts and surgery	0.04	$ (146)
Ovarian Failure	1.24	$ (406,514)
Cost of effort required for food sorting	4.29	$ (272,077)
Cost of monitoring tests	4.29	$ (17,445)
Follow up test		$ (13,204)
Cost of clinical program (share)	4.29	$ (263,309)
Cost of Newborn Screening		$ (2,293,837)
Measures of gain or loss		
Net		**$ 13,550,413**
Net without mortality		$ (3,628,575)
Cost per year of life saved		$ 27,934

The fact that screening may save 4 or 5 lives over a 10-year period dominates the model values. The lives saved generate a present value of $17 million. The model is sensitive to the assigned value of life and contributes to the high standard deviation of the Monte Carlo. If no value were assigned to life then the model would not generate net benefits. The other benefit, reduced cost of clinical identification, does not have much impact.

Testing of all infants generates the largest cost of the program at a present value of $2.3 million. The negative medical outcomes generate over $800,000 in costs. Finally the attendant medical costs of food sorting and following the children medically generate some small costs.

The model is also sensitive to the frequency of the disorder. The DOH defined the statewide frequency based on the structure of the population and the frequencies in sections of the population. The Washington frequency would have to be ¼ the

[23] Insurance agencies on the Newborn Screening Committee asked the DOH to estimate the cost per year of life saved. They indicated that they sometimes use the cost per year of life saved as a means of comparing tests and treatment. The cost per year of life saved is estimated at $28,000 per discounted year. This is well below the $50,000, which the insurers indicate is the point at which they begin to evaluate a procedure more closely.

rate of the rest of the country for the analysis to tip into negative net benefits. Further, the range chosen for the Monte Carlo (.0011% to .0023%) was the widest justified by the literature in order to allow sensitivity testing.

Given the size of the net benefits, only a different value of life would reverse the decision that galactosemia screening will provide net benefits. These net benefits do not count the benefits to children with mild cases of galactosemia (Duarte), for whom lactose elimination is indicated but for whom benefits are less predictable. Further, there is some indication that the number of days of early exposure to galactose may be important for the IQ outcome of some of the children, and this value has not been counted. Thus, unless the reader places a value of less than $1 million on life, which is the low end of the range tested for the Monte Carlo, then expected net benefits will be positive.

Cost Benefit Analysis for Biotinidase Deficiency

Background

Biotinidase deficiency is a rare disorder caused by multiple mutations.[24] Washington expects one in 80,000 infants (0.0012%) to be born with biotinidase deficiency.[25] For Washington this means an average of 10.3 infants would be born with biotinidase deficiency in a ten-year period.

Biotinidase deficiency is a serious metabolic disorder caused by the inability of the body to recycle biotin and reuse it in the body.[26] This results in medical outcomes such as hypotonia, enlarged liver or spleen, ataxia, hearing loss, developmental delay, breathing difficulty, neurological damage, seizures, optic cone atrophy, organic academia, hair loss, rashes, conjunctivitis, and mortality.

In most people the body reuses biotin. Biotinidase deficiency patients can't recycle biotin in the body nor can they release biotin that is bound to proteins in the diet. If the brain can't recycle biotin it may depend on biotin that must cross the blood brain barrier.

Adding free biotin (not bound to protein) to the diet eliminates temporary symptoms such as rapid breathing, conjunctivitis, hypotonia, hepatomegaly, hair loss and rashes. If the infant has experienced reduced biotin for a long period of time, or has had severe metabolic problems with onset of symptoms, some neurological impacts may be permanent. These include developmental delay, hearing loss and optic cone atrophy.

Newborn screening and immediate biotin supplements prevent the negative medical outcomes of biotinidase deficiency.

Benefits of Biotinidase Deficiency Screening

Screening would provide diagnosis weeks before most infants first present with symptoms. Screening would allow an immediate addition of free biotin to the diet. Screening would virtually eliminate mortality and both the immediate and long term impacts of biotinidase deficiency.

- Some infants will not die. Currently in a 10 year period, a statistical mortality of 2.9 children would be expected from the onset of enlarged liver or spleen, breathing difficulty, neurological damage, seizures, or coma. With newborn screening the statistical mortality is reduced by 2.8 children.
- Some infants will avoid brain damage. 1 child would shift from having developmental delay to have a normal IQ outcome.

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[24] Norrgard KJ, Pomponio RJ, Hymes, Wolf B, *Mutations causing profound biotinidase deficiency in children ascertained by newborn screening in the United States occur at different frequencies than in symptomatic children*, Pediatric Research, July 1999, 46(1), 20-27.

[25] This disorder provides an example of a small numbers problem caused by low frequency diseases. Alaska has recently had 2 babies diagnosed despite the small population, where Washington has had none.

[26] Much of the overview information on the function of biotinidase deficiency is drawn from Barry Wolf, *Disorders of Biotin Metabolism*, Chapter 156, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill.

- One child would not have hearing loss.
- Screening is expected to reduce the cost of clinical identification: Currently infants are hospitalized in neonatal intensive care units. With screening there would be an expected reduced cost of stay of $24,000.

Costs of biotinidase deficiency screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs:

- Screening all newborns: The DOH expects to screen 827,000 newborns at a cost of $3.15 each. The expected present value of this cost for a 10-year program is $2.3 million.[27]
- Monitoring tests and clinical program: Children with biotinidase deficiency require occasional monitoring. The expected present value of the added cost for the clinical program for lifetime care is $35,000.[28] The children who screen positive would be expected to testing at $95 each.[29]
- Biotin replacement: The children who would have died will require free biotin medication.

The biotinidase deficiency medical outcomes model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the "front end" or left hand side of the model (see Figure 3). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency**: 1 in 80,000 (.00124%) is the estimated frequency of biotinidase deficiency. For purposes of the Monte Carlo, this frequency was attached to a gamma distribution ranging from .0005% to .0023% with a mean of .00125%.

- **False Negatives**: DOH expects that 0.3% of the biotinidase deficiency cases will be missed by screening due to one of the following reasons: 1. in Washington the failure rate for adequate first blood spots is 0.3%,[30] 2. the infant may have been transfused.

- **True Positives**: This is a function of 1 minus the rate for false negatives.

- **False Positives**: 1 in 80,000 is the estimated number of false positives.[31]

- **Share of profound biotinidase deficiency**: One in 137,000 children is expected to have profound biotinidase deficiency.[32]

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[27] Based on a 3% discount rate. .

[28] Based on current average costs for work with 16 children at the clinical program for Metabolic Disorders at the University of Washington and the estimated share of costs based on the disorder. This includes only the costs of the children who would have died without the screening.

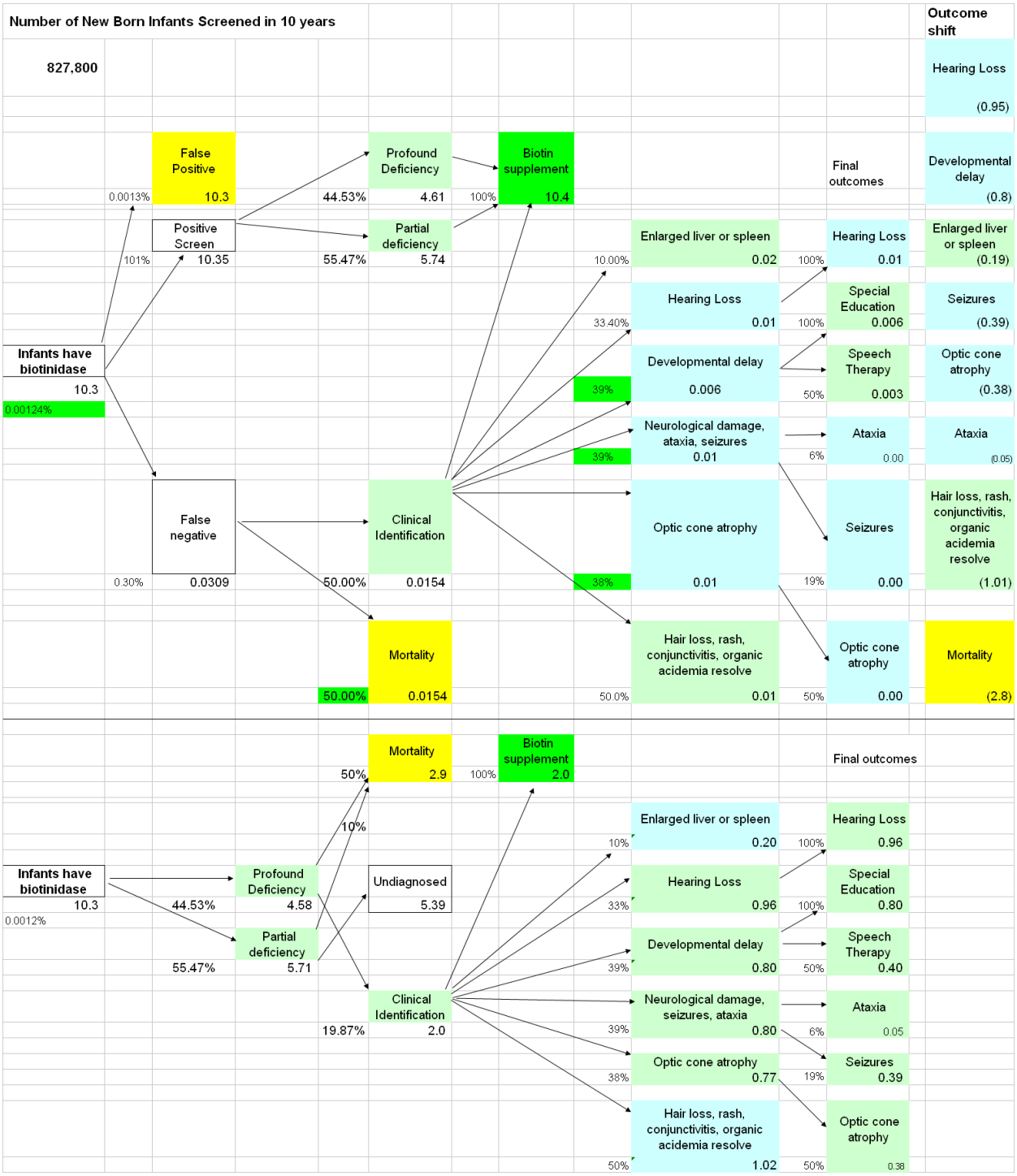
[29] University of Washington, biotinidase quantitation (serum/plasma) (enzyme assay).

[30] Based on the overall failure rate of 1 in 3000 for the two blood spots taken together. Mike Glass

[31] The Magnitude and Challenge of False Positive Newborn Screening Test Results, Charles Kwon, Phillip Farrell, Archives of Pediatric Adolescent Medicine, vol. 154, July 2000

[32] Wolf B, Spencer R, Gleason T, *Hearing loss is a common feature of symptomatic children with profound biotinidase deficiency,* Journal of Pediatrics, Feb. 2002, 140(2) 148-149.

- **Share of partial biotinidase deficiency**: Infants with more moderate forms of biotinidase deficiency are the remaining portion of the biotinidase deficient population.



- **Mortality** is estimated at .5 for the children who are clinically diagnosed, based on recent experience at the University of Washington. Children, who have been screened, are diagnosed more rapidly as the results become available well before the child is presenting with symptoms. The estimated mortality for true positive screened infants is 0% because treatment is very simple and compliance is good.

- **Neurological damage, seizures, ataxia, developmental delay outcomes**: Under clinical diagnosis less than half of the children would be expected to have neurological damage yielding developmental delay, and/or seizures or ataxia. The range depends on which of several forms of the disorder the children have. The mean is set at 39% with a 6% standard deviation for the Monte Carlo and an upper bound of 50% for both sets of outcomes.[33]

- **Special education or speech therapy**: Some of the children with developmental delay may receive special education or speech therapy. These are not included as separate value in the cost estimate but are presented as estimates.

- **Optic Cone Atrophy**: In 25% to 50% of the clinically diagnosed patients, optic cone atrophy and vision loss may result from late diagnosis. A normal distribution with a mean of 37.5% and a standard deviation of 3% was set for the Monte Carlo with an upper bound of 50%.

- **Hearing Loss**: 75% of the clinically diagnosed children with profound biotinidase deficiency would be expected to have hearing loss of varying degrees. This is 38% of the patient population. With screening the loss is eliminated.

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is described in the prior section on Galactosemia.

- Minor **neurological damage that reduces IQ** is described in the prior section on Galactosemia.

- **Hearing Loss** costs are estimated at $300,000 per case.[34]

- **Optic cone atrophy, ataxia and seizures** are not valued because of the possibility that there are overlapping distributions of IQ loss and ataxia and seizures. Optic cone atrophy is not valued because the descriptors in the biotinidase deficiency literature don't yield sufficient information on the degree of vision loss.

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[33] Wide bounds were set because the percentage estimates were based on a sample of 120 patients and the outcome percentages would shift based on a small number of patients having a different outcome.

[34] Amanda A. Honeycutt, Scott D. Grosse, Laura J. Dunlap, Diana E. Schendel, Hong Chen, Edward Brann, and Ghada al Homsi, Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment Research in Social Science and Disability, Vol. 3, 207-228, 2003

Net Present Value of Biotinidase Deficiency Screening Benefits

The addition of biotinidase deficiency screening in Washington generates net benefits of $9.6 million. The Monte Carlo indicates a range of minus $1 million to $29 million, with a mean of $9.6 million and a standard deviation of $4 million.[35]

Estimating Net Benefits		
Gain		**Expected Values**
Developmental delay	(0.79)	$ 229,529
Mortality avoided	(2.85)	$ 11,389,861
Reduced cost of clinical Identification	(2.0)	$ 24,353
Optic cone atrophy	(0.38)	Overlapping conditions - no value added
Seizures	(0.39)	Overlapping conditions - no value added
Ataxia	(0.05)	Overlapping conditions - no value added
Hearing Loss	(0.95)	$ 309,772
Cost		
Cost of vitamin biotin supplement	2.85	$ (10,335)
Cost of Clinical Program		$ (34,915)
Testing Costs		$ (1,562)
Cost of Newborn Screening		$ (2,293,837)
Net		**$ 9,612,865**
Net without Mortality		$ (1,776,996)
$/year of life saved		$ 27,442

The fact that screening may save 2 or 3 lives over a 10-year period dominates the model values. The lives saved generate a present value of $11 million. The model is very sensitive to the assigned value of life and this contributes to the high standard deviation of the Monte Carlo. If no value were assigned to life then the model would not generate net benefits. The other benefits in the form of reduced costs of optic cone atrophy, IQ loss and developmental disability, seizures, hearing loss, ataxia, and clinical identification savings, do not have as much impact.

Testing of all infants generates the largest cost of the program at a present value of $2.3 million. Finally the attendant medical costs of biotin and following the children medically generate some small costs. The model is also sensitive to the frequency of the disorder. The DOH defined the statewide frequency based on seven years of frequency data from Virginia.[36] The Washington frequency would have to be less than 1/3 the rate for Virginia for the analysis to tip into negative net

[35] Insurance agencies on the Newborn Screening Committee asked the DOH to estimate the cost per year of life saved. They indicated that they sometimes use the cost per year of life saved as a means of comparing tests and treatment. The cost per year of life saved is estimated at $27,000 per discounted year. This is well below the $50,000, which the insurers indicate is the point at which they begin to evaluate a procedure more closely.

[36] New England Journal of Medicine 1985, Thibodeau, Wolf 8/20/99 Department of Human Genetics and pediatrics Medical College of Virginia 8048289632 and Newborn Screening for biotinidase Deficiency: Results of a one year Pilot Study, Heard et al. Reprint Dept. of Human Genetics, Medical College of Virginia, paper 267.

benefits. Further the range for the Monte Carlo (.00058% to .0023%) was the widest justified by the literature.

Given the size of the net benefits, only a different value of life would reverse the decision that the biotinidase deficiency screening will provide net benefits. Thus, unless the reader places a value of $1 million or less on life, which is the low end of the range tested for the Monte Carlo, then expected net benefits will be positive.

Cost Benefit Analysis for MCADD

Background

Medium chain acyl-CoA Dehydrogenase deficiency (MCADD) is a rare disorder. [37] Over 90% of the children have a single missense mutation in the MCAD gene but MCADD may be caused by several other mutations.[38] DOH expects one in 20,000 infants (0.005%) would be born with MCADD. For Washington this means about 35 infants would be born with MCADD in a ten-year period.

MCADD is a serious metabolic disorder caused by the inability of the body to process medium chains of fats. Extended fasting brought on by flu or excitement or a simple failure to eat can cause a build up of the medium chain fats to toxic levels. When fasting occurs, the resulting buildup of toxins can cause severe neurological trauma resulting in the hospitalization or death of the child. MCADD is thought to be one of the reasons for sudden infant death.

If an undiagnosed infant or child with MCADD is put on a glucose drip they will recover and may not be diagnosed. This may reoccur until a diagnosis is made, until the child dies or the child may remain undiagnosed.

Benefits of MCADD Screening

Screening would provide diagnosis weeks before most infants first present with symptoms. Screening would allow the family to react early when fasting occurs. Screening would virtually eliminate mortality and both the immediate and long term impacts of MCADD. The modeled impacts are as follows:

- Some infants will not die. Currently in a 10 year period, a statistical mortality of 7 children would be expected from fasting and rapid decompensation. With newborn screening the statistical mortality is reduced to 0.14 children. The estimated value of reduced statistical mortality is $28 million.
- 9 children will avoid neural damage, which may cause both single and overlapping problems. 2 infants may avoid cerebral palsy. 4 children may avoid global developmental disabilities. 6 children may avoid speech and language delay. One child may avoid aphasia. 3 children may avoid ADD. 4 children may avoid seizures. 1 child

[37] Much of the overview information on the function of MCAD is drawn from CR Roe and J Ding, *Mitochondrial Fatty Acid Oxidation Disorders*, Chapter 101, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill. Iafolla AK, Millington DS, Chen YT, Ding JH, Kahler SG, Roe CR: Natural course of medium chain acyl-CoA dehydrogenase deficiency. *American Journal of Human Genetics* 49(Suppl):99, 1991, Iafolla AK, Thompson RT, Roe CR: Psychodevelopmental outcome in children with medium chain acyl CoA dehydrogenase deficiency. *American Journal of Human Genetics* 51:A351, 1992, Iafolla AK, Thompson RJ, Roe CR: Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *Journal of Pediatrics* 124:409-15, 1994, Wilken B, Hammond J, Silink M: Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Archives of Disease in Childhood* 70:410-412, 1994 and Pollitt RJ, Leonard JV: Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK. *Archives of Disease in Childhood* 79:116-119, 1998 Touma EH and Charpentier C: Medium chain acyl-CoA dehydrogenase deficiency. Archives of Disease in Childhood 67:142-145, 1992.

[38] *The molecular basis of medium chain acyl-CoA dehydrogenase (MCAD) deficiency in compound heterozygous patients: is there a correlation between genotype and phenotype?* BS Andresen, P Bross, S Udvari, J Kirk, G Gray, S Kmoch, N Chamoles, I Knudsen, V Winter, B Wilken, I Yokota, K Hart, S Packman, JP Harpey, JM Saudubray, DE Hale, L Bolund, S Kolvraa, N Gregersen, Human Molecular Genetics, 1997, pgs 695-707.

may avoid headaches. The estimated value of avoiding this range of disabilities is approximately $4 million.

- 4 children may avoid muscle weakness. 2 children may avoid behavioral problems. One child may avoid chronic abdominal pain.
- Screening is expected to reduce the cost of clinical identification: Currently infants or children may be hospitalized repeatedly until they are diagnosed. The expected reduced cost of stays is $300,000 based on an estimated 4 days of hospitalization at $3,000 per day.[39]

Costs of MCADD screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs:

- **Screening all newborns**: The DOH expects to screen 827,000 newborns at a marginal cost of $12 each. This cost is assumed to provide a conservative[40] estimate of the cost. The expected present value of this cost for a 10-year program is $8.7 million.[41]
- **Hospitalization for periods of fasting**. The children who would have died will require occasional hospitalization and a glucose drip during periods of fasting. The estimated cost of $800,000 is based on a 72-year life-span and hospitalization once every 3 years. The estimated cost of hospitalization per incident is $12,000. This estimate is probably high but is certainly conservative.
- **Clinical Program**: Children, who test positive, including the false positives, will need confirmatory testing at a cost of $1100.[42] In addition the children with MCADD identified through the screening program will require testing and the use of the clinical program. The children who would have died without the screen will add to the cost of this program. The estimated cost per child per year is approximately $300 and the present value is $85,000.

The MCADD medical outcomes model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the "front end" or left hand side of the model (see Figure). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency**: 1 in 20,000 (0.005%) is the estimated frequency of MCADD. This frequency does not include the non-clinical forms of MCADD, which are also identified by the screening. These forms are not generally lethal and may not have any impact except under extreme conditions. The non-clinical form has an estimated frequency of 1 in 43,000 and is separated from the more typical MCADD. No costs beyond the screen

[39] This value may be low or high. DOH does not have reasonable data on duration and frequency of stays for a population or for a sample. The Organic Acidemia Association has provided anecdotal data of costs prior to diagnosis far larger than this, ranging from $0 to $790,000 for a case which causes complications. It is however conservative in that it is probably biased against the rule.

[40] Conservative for this analysis means that if bias exists, it is biased against the rule.

[41] Based on a 3% discount rate.

[42] Urine organic acid analysis, 297.55, Mutation analysis, 245, Plasma carnitine analysis, 164, Acylcartinine analysis, 164, Acylglycine urine analysis, 255.30.

and initial testing and no benefits are modeled for identification of the non-clinical MCADD.

- **False Negatives**: DOH expects that 2% of the MCADD cases will be missed by screening because in Washington the failure rate for blood spots is .3%. In addition, infants with MCADD who have undergone blood transfusions may also have false negative test results.

- **True Positives**: This is a function of 1 minus the rate for false negatives.

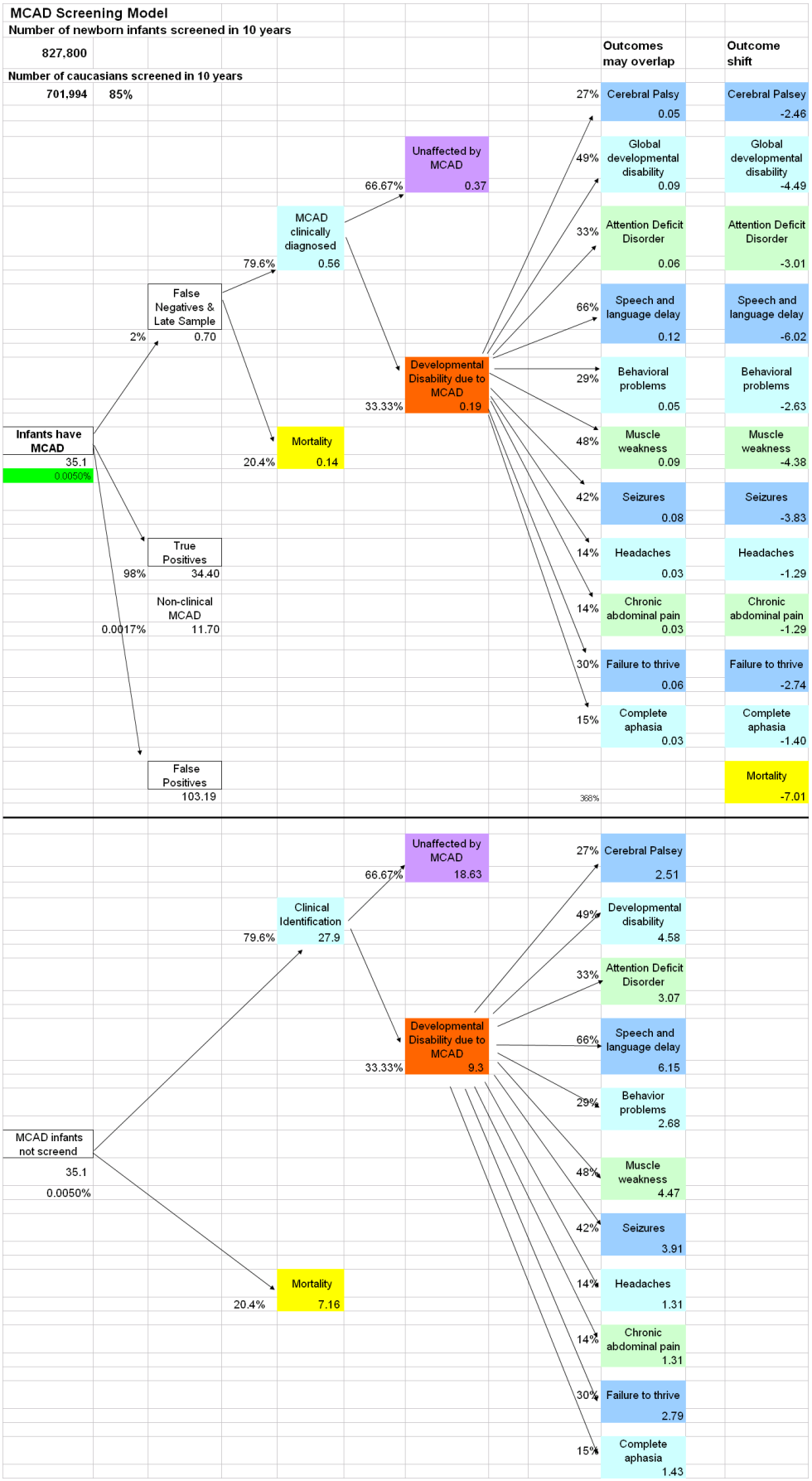
- **False Positives**: DOH expects 3 false positives for every true positive.

- **Share of mortality**: DOH expects that 20% of the infants and children with MCADD currently die. This level of mortality is associated only with the clinical form of MCADD.[43] None of the infants identified through screening are likely to die if they avoid fasting and receive IV glucose when they are sick and unable to eat.

- **Share clinically diagnosed**: Currently infants who do not die are clinically diagnosed. The model estimates this based on the number of children that do not die during clinical presentation of the disorder. This is 80% for the status quo. With screening 98% of children with MCADD would be identified by the screen and 1.6% through clinical diagnosis.

- **Disability outcomes**: Approximately 1/3 of the children diagnosed clinically are expected to have developmental disability due to the neurological trauma during the initial onset of symptoms. Many will have overlapping problems.

[43] If the non-clinical form of MCAD is added to the clinical population then the mortality rate is 16%.


MCAD Screening Model
Number of newborn infants screened in 10 years
827,800
Number of caucasians screened in 10 years
701,994
85%
Infants have MCAD
35.1
0.0050%
False Negatives & Late Sample
2%
0.70
True Positives
98%
34.40
Non-clinical MCAD
0.0017%
11.70
False Positives
103.19
MCAD clinically diagnosed
79.6%
0.56
Mortality
20.4%
0.14
Unaffected by MCAD
66.67%
0.37
Developmental Disability due to MCAD
33.33%
0.19
Outcomes may overlap
Outcome shift
27% Cerebral Palsy 0.05 Cerebral Palsey -2.46
49% Global developmental disability 0.09 Global developmental disability -4.49
33% Attention Deficit Disorder 0.06 Attention Deficit Disorder -3.01
66% Speech and language delay 0.12 Speech and language delay -6.02
29% Behavioral problems 0.05 Behavioral problems -2.63
48% Muscle weakness 0.09 Muscle weakness -4.38
42% Seizures 0.08 Seizures -3.83
14% Headaches 0.03 Headaches -1.29
14% Chronic abdominal pain 0.03 Chronic abdominal pain -1.29
30% Failure to thrive 0.06 Failure to thrive -2.74
15% Complete aphasia 0.03 Complete aphasia -1.40
Mortality -7.01
368%
MCAD infants not screend
35.1
0.0050%
Clinical Identification
79.6%
27.9
Mortality
20.4%
7.16
Unaffected by MCAD
66.67%
18.63
Developmental Disability due to MCAD
33.33%
9.3
27% Cerebral Palsy 2.51
49% Developmental disability 4.58
33% Attention Deficit Disorder 3.07
66% Speech and language delay 6.15
29% Behavior problems 2.68
48% Muscle weakness 4.47
42% Seizures 3.91
14% Headaches 1.31
14% Chronic abdominal pain 1.31
30% Failure to thrive 2.79
15% Complete aphasia 1.43

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is covered in the Galactosemia section above.

- **Neural damage that produces mental retardation and global developmental disabilities** is valued at $870,000.[44] The model then attaches values only to those children with developmental disabilities.

- **Cerebral palsy** is valued at $ 800,000.[45] The model then attaches values only to the percentage share of children with cerebral palsy who would be unlikely to have the overlapping, higher cost mental retardation.

- Other Disabilities. The values used for mental retardation and cerebral palsy are based on data which include patients with multiple disabilities. Further, the model itself predicts overlapping disabilities. Counting the added disabilities may in some cases have involved double counting and is not conservative. Therefore DOH did not add values to the other disabilities. This makes the model extremely conservative in that the disabilities of 3 children who would be predicted to have experienced other disabilities are not counted.

[44] Amanda A. Honeycutt, Scott D. Grosse, Laura J. Dunlap, Diana E. Schendel, Hong Chen, Edward Brann, and Ghada al Homsi, Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment Research in Social Science and Disability, Vol. 3, 207-228, 2003

[45] ibid

Net Present Value of MCADD Screening Benefits

The addition of MCADD screening in Washington generates net benefits of $23 million. The Monte Carlo indicates a range of $3.6 million to $48 million and a standard deviation of $8 million. The fact that screening may save seven lives over a 10-year period dominates the model values. The seven lives saved generate a present value of $28 million. The model is sensitive to the assigned value of life and this contributes to the high standard deviation of the Monte Carlo. If no value were assigned to life then the model would not generate net benefits. The low end estimate for the value of life for the Monte Carlo is $3.6 million and this still generates positive net benefits. This indicates that the reader would have to value life at below $1 million in order to find negative net benefits. The avoided developmental disabilities alone do not offset the costs.

Testing of all infants generates the largest cost of the program at a present value of $8.7 million. This estimate was based on a per unit use contract. This type of contract allows the state free use of the machinery and payment is made through a per-unit cost of chemical pack payments. Finally, the attendant medical costs of treating the children during illness that causes fasting and following the children medically generate almost $1 million in costs. The cost per year of life saved is approximately $48,000.

Estimating Net Benefits		
Gain		**Expected**
	Adjusted population	
All Developmental Disabilities	(4.49)	$ 3,918,735
Mortality avoided	(7.01)	$ 28,057,737
Reduced cost of clinical Identification	(27.4)	$ 328,599
Cerebral Palsey	(2.46)	$ 316,349
Attention Deficit Disorder	(3.01)	overlap no value included
Behavioral problems	(2.63)	overlap no value included
Speech and language delay*	(6.02)	overlap no value included
Complete aphasia	(1.40)	overlap no value included
Muscle weakness	(4.38)	overlap no value included
Seizures	(3.83)	overlap no value
Headaches	(1.29)	overlap no value
Chronic abdominal pain	(1.29)	overlap no value
Failure to thrive	(2.74)	overlap no value included
Cost		
Hospitalization for illness-vomiting	7.01	$ (848,635)
Clinical testing	149.99	$ (99,281)
Cost of Clinical Program	(7.01)	$ (215,026)
Cost of Newborn Screening		$ (8,727,769)
Net		**$ 22,730,708**
Net without mortality		$ (5,327,029)
$/year of life saved		$ 48,168

The model is also sensitive to the frequency of the disorder. The DOH defined the statewide frequency based on frequencies for the Caucasian population. The Washington frequency would have to be ½ the national estimated frequency for the analysis to tip into negative net benefits.

Given the size of the net benefits, only a different value of life would reverse the decision that the MCAD deficiency screening will provide net benefits. Thus, unless the reader places a value of $1 million or less on life, which is the low end of the range tested for the Monte Carlo, then expected net benefits will be positive.

Cost Benefit Analysis for Homocystinuria

Background

Homocystinuria is very rare. Only 600 cases have been available for study since it was discovered in the 1960s. Washington expects one in 168,000 infants (0.0006%) to be born with homocystinuria.[46] For Washington this means an average of 4.9 infants would be born with homocystinuria in a ten-year period.

Homocystinuria is a serious metabolic disorder caused by the inability of the body to process methionin, which is in some proteins.[47] In most people the transulfuration pathway converts sulfur into cystiene. The primary part of this pathway has 14 separate reactions that may be affected. Multiple genetic mutations cause flaws or failures of these reactions. For one of these reactions there are 9 separate disorders that have been identified. However, most of the children with homocystinuria have Cystathionine ß-synthase deficiency. Homocystine and its metabolites accumulate in the body. This results in medical outcomes such as artery and vein problems (thromboembolic events), retardation, marfan and osteoporosis, ectopia lentis, seizures, personality disorders, and early mortality.

The infants fall into two broad categories.

- **B6 responsive** infants improve if they are given vitamin B6 in large doses in their diets. They generally do very well, except that the doses of B6 sometimes cause ataxia and minor neural damage. Some of these children will also need betaine. Most will have some intolerance of methionine and require small meals. Only 10% of these children will be caught by current newborn screening tests[48] but 90% would be caught by tandem mass spectrometry (MS/MS).[49] These are the children that respond best to treatment and early treatment is important.

- **B6 non-responsive** infants don't respond to B6 treatment and methoinine must be removed from the diet. This is difficult for children who have experienced a normal diet and so early treatment works better. Further, methionine should be removed from the diet as soon as possible to avoid brain damage. These children develop problems rapidly and the blood will have sufficient indicators that it will be caught by both current technology and by MS/MS. These children are already affected when the first bloodspot is taken. The results come in as the child presents and action can be taken more rapidly.

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[46] Washington has generally had 4 or 5 non-responsive children under 20 (Ron Scott, University of Washington). The model rate of 1/168,000 is extrapolated from this number. It is close to the average frequency estimated by the Department Of Health Newborn Screening Program based on data from: National Newborn Screening and Genetic Resource Center, National Newborn Screening Report –1996 (October 2000) – 1997 (May 2001) and – 1998 (December 2001) NNSCRC, Austin TX (Mike Glass, DOH).

[47] Much of the overview information on the function of Homocystinuria is drawn from S Harvey Mudd, Harvey L Levy, Jan P. Kraus, *Disorders of Transsulfuration,* Chapter 88, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill.

[48] One individual has questioned this low value.

[49] Susan Panney, Maryland Newborn Screening program, discussion with Scott Grosse, CDC, 5/7/2002, only one of 8 cases was a responder.

Benefits of Homocystinuria Screening

Screening would provide diagnosis just as the infant first presents with symptoms. Screening would allow an immediate addition of B6 to the diet and/or shift away from methionine in the diet. Screening would reduce the constellation of symptoms, risk of mortality, and the immediate impact of high doses of homocystine and its metabolites.

- Some infants will not die. Currently in a 10 year period, a reduced statistical early mortality of .23 children would be expected from eliminating the onset of reactions to homocystine.
- Some infants will avoid brain damage. All infants should shift up into a higher category of mental function. One infant would avoid significant mental retardation. Two infants would avoid mild retardation. Two or more of these infants with earlier diagnosis would avoid brain damage and would have a normal IQ. One infant would avoid a typical personality disorders.
- One child would not have ectopia lentis.
- Finally, there would be a reduction or significant postponement of thromboembolic events for .17 children on average, which causes the early mortality reduction listed above.
- Screening is expected to reduce the cost of clinical identification: Currently most homocystinuric infants are hospitalized in neonatal intensive care units. With screening there would be an expected reduced cost of stay of $46,000.[50]

Costs of Homocystinuria Screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs and negative medical outcomes for children who would otherwise have died:

- Screening all newborns: The DOH expects to screen 827,000 newborns at a cost per child of $4 each for current chemical tests or $1.10 if there is a MS/MS on site. The expected present value of this cost for a 10 year program is $2.9 million under current technology and $800,000 for MS/MS.[51]
- Clinical program: The screening will make little difference to the cost of the clinical program because most of the impact will be on the medical outcome rather than mortality. The children who would have died would be expected to need the clinical program that currently monitors the blood work, trains families how to select food, explains test results, and intervenes with the child when he or she decides to eat inappropriately. The average cost per year for clinical work on this disorder is higher than most at $10,000 per year. Diagnostic testing runs $305 per child. Follow-up testing runs $285 per year per child. However, the number of children who do not die because of screening is so small that the estimated increase in costs and follow-up testing is under $100,000.
- The B6 non-responsive children who do not die will also require dietary adjustment. Given that the program would save on average .11 such children every 10 years, the value

[50] The expected reduction in number of days in the hospital is 7. Not all days are spent in the Neonatal intensive care Unit; therefore the estimated cost is $1,600 per day.

[51] Based on a 3% discount rate. Note: Homocystinuria does not create sufficient change in outcomes to justify purchase of MS/MS technology. If MS/MS is already purchased for another disorder, then Homocystinuria can be added to the chemical package for a run that is already taking place. Thus the marginal cost is the cost of test chemicals, additional standards and controls, interpretation of test results, reporting and follow up of abnormal results.

in the model is averaged between the food and supplements for non-responsive children and supplements for responsive children. The estimated cost is $12,000.

The Homocystinuria Medical Outcomes Model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the "front end" or left hand side of the model see Figure 1). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency**: 1 in 168,000 is the estimated frequency of homocystinuria (.0006). This should be regarded as a conservative (low) frequency since it does not include unidentified mortality.
- **False Negatives**: For a screening program, DOH expects that 10% of the B6 responsive homocystinuria cases will be missed by screening.
- **True Positives**: Without screening only 5% of the children are diagnosed in the first 6 weeks. 95% of the children are later identified in a clinical setting after some damage has already occurred. For the screening portion of the model this is a function of 1 minus the rate for false negatives and depends on whether or not the child is B6 responsive.
- **False Positives**: For a screening program Washington expects that the tests will generate a false positive rate of 2 to 1 once the tests are calibrated properly. The first year or two there may be a higher rate because the program will try to avoid missing a child during the period when the tests are still being calibrated.[52]
- **Share of B6 responsive infants**: There is a small numbers problem in estimating this value. Washington is rounding off the reported 43%[53] to 50%.[54]
- **Share of B6 non-responsive**: The infants who do not respond to B6 are either non-responsive or only partially responsive and must have methionine in the diet reduced. In the model this is 50%.
- **Mortality** is estimated based on Mudd's compiled numbers for late and early detection, for B6 responsive and non-responsive children.[55] A reduction from the early statistical mortality of .22 is estimated for a 10 year period for each group.
- **Diet Compliance**: Children who take the B6 or who comply with dietary restrictions have better outcomes. Generally compliance is excellent for the B6 responsive group. For the non-responsive group compliance is difficult because the diet is not desirable. The model uses 32% as the estimate for non-compliance.[56] There may be much better compliance for neonates who do not become accustomed to a normal diet. Thus the estimated non-compliance rate in the model, which is based in part on children who were identified late, may be high. [57]

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[52] Mike Glass, Washington Newborn Screening program.

[53] S Harvey Mudd, Flemming Skovby, Harvey L. Levy, Daren D. Gettigrew, Bridget Wilcken, Reed E Pyeritz, G. Andria, Godfried H. J. Boers, Irvin L. Bromberg, Roberto Cerone, Brian Fowler, H Grobe, Hildgund Schmidt, Leslie Schweitzer, *The Natural History of Homocystinura Due to Cystathioine B- Synthase Deficiency*, American Journal of Human Genetics, 37,[pgs 1-31, 1985.

[54] This may create a minimal bias in favor of the rule change; however the number of children is insufficient to distinguish between 50% and 43%. Personal conversation with Ron Scott.

[55] Ibid.

[56] Yap S, Rushe H, Howard PM, Naughten ER, *The Intellectual abilities of early treated individuals with pyridoxine-nonresponsive homocystinuria due to cystathionine beta synthase deficiency*, Journal of Inherited Disease, 2001, Aug 24 (4):437-47.

[57] This may bias the model against the rule change.

- **IQ outcomes**: IQ outcomes depend on the timing of intervention, the compliance of the child, and whether the child is B6 responsive. The patient does better if the disorder is discovered early, if they are B6 responsive and if they stick to the treatment. The probabilities for varying levels of IQ loss for B6 non-responsive children were drawn from Yap (2001).[58] The remaining probabilities in the model were drawn from Mudd [85].[59] Given expected frequencies, 2.6 additional children would have normal IQs.
- **Ectopia Lentis (lens separation)**: For homocystinurics that don't maintain treatments, it is only a matter of time to the event. B6 responsive patients who are detected early and maintain compliance have no impact. 19% to 20% of B6 responsive patients who are detected late but comply with treatment generate lens separation. Early treated, non-responsive patients have a 15% chance of lens problems, where the late treated children have a 53% chance. [60] Early detection is expected to eliminate one lens separation.
- **Thrombo-embolic Events**: For homocystinurics that don't maintain treatments it is only a matter of time to a thrombo-embolic event.[61] Without treatment there is only a 33% chance that they will reach the age of 44 without one. With treatment, the non-responders have a 5% chance of an event if they are discovered late, where responders have a 2.5% chance of an event if they are detected late, but in both cases the event is postponed. With early detection and full treatment the expected incidence is 0. Screening is expected to reduce the number of event onsets by .17 children.
- **Personality Disorders**: 40% or more of B6 responsive patients and 70% of non-responsive patients suffer from psychiatric abnormalities including personality disorders, behavioral problems, depression, and obsessive compulsive disorders.[62] These problems resolve with treatment unless permanent brain damage has been done.[63] The model predicts early screening will prevent one patient from having these problems.
- **Marfan and Osteoporosis**: Good treatment postpones marfan and osteoporosis, which develops slowly. Children may benefit from screening, but the model does not predict a change in the number of cases.
- **Seizures**: Untreated children may begin to have seizures. The time of onset is earlier for the non-responsive children.[64] Once they start, the seizures do not reduce with treatment for the non-responsive children but there is some indication that they improve for the B6

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[58] *The intellectual abilities of early-treated individuals with pyridoxine-nonresponsive homocystinuria due to cystathionine beta-synthase deficiency*, Yap S, Rushe H, Howard PM, Naughten ER, Journal of Inherited Metababolic Disabilities, 2001 Aug, *24(4):437-4*, "The newborn screened, good compliance group (n=13) with a mean age of 14.4 years (range 4.4-24.9) had mean full-scale IQ (FIQ) of 105.8 (range 84-120), which the poorly compliant group (n=6) with a mean age of 19.9 years (rage13.8-25.5) had a mean FIQ of 80.8 (range 40-103). The control group (n=10) with a mean age of 19.4 years (range 9.7-32.9) years had a mean FIQ of 102 (range 76-116). The two late-detected patients aged 18.9 and 18.8 years had FIQ of 80 and 102, while the two untreated patients aged 22.4 and 11.7 years had FIQ of 52 and 53, respectively.

[59] S Harvey Mudd, Flemming Skovby, Harvey L. Levy, Daren D. Gettigrew, Bridget Wilcken, Reed E Pyeritz, G. Andria, Godfried H. J. Boers, Irvin L. Bromberg, Roberto Cerone, Brian Fowler, H Grobe, Hildgund Schmidt, Leslie Schweitzer, *The Natural History of Homocystinura Due to Cystathioine B- Synthase Deficiency*, American Journal of Human Genetics, 37,[pgs 1-31, 1985.

[60] Ibid see table 5.

[61] The event may be caused by a mix of the following oxidant stress and transmethylation related disorders: Thromboembolism, Atherosclerosis, Platelet adhesiveness, Endothelial Cellular effects, Coagulation problems, Plasma Lipoprotein binding.

[62] S Harvey Mudd, Flemming Skovby, Harvey L. Levy, Daren D. Gettigrew, Bridget Wilcken, Reed E Pyeritz, G. Andria, Godfried H. J. Boers, Irvin L. Bromberg, Roberto Cerone, Brian Fowler, H Grobe, Hildgund Schmidt, Leslie Schweitzer, *The Natural History of Homocystinura Due to Cystathioine B- Synthase Deficiency*, American Journal of Human Genetics, 37,[pgs 1-31, 1985.

[63] Ron Scott, University of Washington.

[64] Mudd (1985) indicates that the nonresponsive children have a 20% chance of having seizures by age 12 where this rate is delayed to age 21 for B6 responsive children.

Responsive children. The rates for non-responsive children detected through screening are adjusted to 1/4th of the rate for the late detected children.[65] The rates for B6 responsive children detected through screening are set at zero. The model predicts that screening will reduce by .5 the number of cases of seizures.

- **Other Health Issues**: There may also be problems with connective tissue, hypopigmentation, thin skin, liver, hernia, myopathy, or the endocrine system.

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is covered under Galactosemia above.
- **Neural damage that reduces IQ** is covered under Galactosemia above.
- **Lens surgery** costs are estimated at $3,000 and the present value is based on likely age of ectopia lentis.
- **Seizures** are valued at $211,000 for a 10 year period. This value is based on reduced mobility and inability to drive a car.[66] The present value is based on only 10 years of loss. The range of values for the Monte Carlo is based on a Weibull distribution with a mean of $211,000, a minimum of $124,000 and a maximum of $300,000.

[65] This estimate based on Mudd (1985) may be subject to significant error. Only 1 of 4.2 expected seizure onsets occurred. This estimated value clearly has a small numbers problem.

[66] Valuing Health for Policy: an economic approach, eds. George Tolley, Donald Kenkel, and Robert Fabian, University of Chicago Press, 1994, values indexed to 2001. This value is lower than values generated for cerebral palsy by Amanda A. Honeycutt, Scott D. Grosse, Laura J. Dunlap, Diana E. Schendel, Hong Chen, Edward Brann, and Ghada al Homsi, Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment Research in Social Science and Disability, Vol. 3, 207-228, 2003. The value is further lowered by using the 10 year present value rather than a full lifespan. Although the literature indicates the seizures do not reduce with treatment, Ron Scott, University of Washington, indicates that he has had success with some patients with seizures. Thus the lower figure is used.

Homocystinuria Screening Model																													
												Personality Disorders		Mortality		Seizure		IQ				IQ Point Reduction*							
Number of New Born Infants Screened in 10 years						Lens Dislocation		Thromboembolic Events	Osteo Porosis	Rates**	Personality Disorders	Rates	Early Mortality	Rates	Seizures		Normal IQ Range		14.80		25.00		53.30						
827,800				0.99	Compliant																								
			0.05 Early detect		0.1216	0		0		0	0	0	0	0	0	100%	0.1216												
No		50% B6 responsive		1%	Non compliant																								
Screen		2.4567	0.1228		0.0012	0.0004		0.0002	0.0007	0.41	0.0005	0.0588	0.0001	0.0840	0.0001	51%	0.0006	11%	0.0001	33%	0.0004	5.2%	0.0001						
				0.99	Compliant																								
			0.95 Late detect		2.3105	0.4443		0.0685		0.18	0	0.0125	0.0289	0.0840	0.1941	51%	1.1761	11%	0.2588	33%	0.7555	5.2%	0.1201						
			2.3339	1%	Non compliant																								
					0.0233	0.0097		0.0034	0.0129	0.41	0.01	0.2250	0.0053	0.1680	0.0039	0	0.0000	62%	0.0145	33%	0.0076	5.2%	0.0012						
Infants have homocystinuria																													
4.91																													
0.0006%				0.68	Compliant																								
No		B6 non-50% responsive	0.05 Early detect		0.0840	0.0108		0.0000		0	0	0.0000	0.0000	0.0557	0.0047	100%	0.0840												
Screen		2.4567	0.12	32%	Non compliant																								
					0.0388	0.0161		0.0027	0.0249	0.73	0.028	0.0122	0.0005	0.2340	0.0091					100%	0.0388								
				0.68	Compliant																								
			0.95 Late detect		1.5969	0.8598		0.0779		0.43	0.690	0.0244	0.0389	0.2340	0.3737			100%	1.5969										
			2.33	32%	Non compliant																								
					0.7370	0.2608		0.0867	0.4726	0.73	0.538	0.2250	0.1658	0.2340	0.1725									100%	0.7370				
			N			1.6020		0.2394	0.5110		1.69		0.2395		0.7580		1.3823		1.8703		0.8024		0.8584						
				0.99	Compliant																								
			90% Screened		2.1889	0		0		0.0	0.0	-	-	-	-	100%	2.1889												
Screen		50% B6 responsive	2.21	1%	Non compliant																								
		2.4567			0.0221	0.0077		0.0027	0.0122	0.41	0.01	0.0588	0.0013	0.0840	0.0019	51%	0.0113	11%	0.0025	33%	0.0072	5%	0.0011						
				0.99	Compliant																								
			10% Late detect		0.2432	0.0468		0.0072		0.18	0	0.0125	0.0030	0.0840	0.0204	51%	0.1238	11%	0.0272	33%	0.0795	5%	0.0126						
			0.25	1%	Non compliant							-																	
					0.0025	0.0010		0.0004	0.0014	0.41	0.0010	0.2250	0.0006	0.1680	0.0004	0%	0.0000	62%	0.0015	33%	0.0008	5%	0.0001						
Infants have homocystinuria			False Positives																										
4.91			200% 9.8																										
				0.68	Compliant																								
Screen		B6 non-50% responsive	99.97% Screened		1.6804	0.2168		0		0	0	-	-	0.0557	0.0936	100%	1.6804												
		2.4567	2.46	32%	Non compliant																								
					0.7756	0.3222		0.0549	0.4973	0.73	0.57	0.0122	0.0095	0.2340	0.1815					100%	0.7756								
				0.68	Compliant																								
			0.03% Late detect		0.0005	0.0003		0.0000		0.43	0.00	0.0244	0.0000	0.2340	0.0001			100%	0.0005										
			0.0007	32%	Non compliant																								
					0.0002	0.0001		0.0000	0.0001	0.73	0.00	0.2250	0.0001	0.2340	0.0001									100%	0.0002				
			N			0.5949		0.0652	0.5110		0.62		0.0144		0.2980		4.0044		0.0317		0.8631		0.0142						
NET CHANGE			**NET CHANGE**			**(1.01)**		**(0.17)**	-		**(1.07)**		**(0.23)**		**(0.46)**		**2.62**		**-1.84**		**0.06**		**-0.84**						

- **Personality Disorders** are valued at $500,000. This is based on a depression and anxiety value with lack of friends and contacts.[67] The present value is based on only 10 years of loss.[68] Note: this value has a significant impact on the total value and it is unclear from the data whether there is double counting with respect to the other neurological impacts.
- **Thromboembolic event onset** is priced at $54,000. The events may have a wide range of origins and cost impacts, including zero cost if they are immediately fatal. They are therefore valued using indexed total costs estimated for transposition. Transposition is the lowest of the costs for four potential cardiovascular developmental disorders presented by the EPA.[69]
- The **Newborn Screening** cost is estimated at $1.10 per child if MS/MS is available and at $4 per child given traditional technology**.** The expected present value of this cost for a 10-year program is $2.9 million under current technology and $800,000 for MS/MS.[70]
- **Clinical Programs** track the patient. The increased present value of costs for the lifespan of a patient is $3 million. B6 non-responsive homocystinuria is more complicated and difficult to manage than other disorders.[71] Given that most patients would not die and would be in the program anyway, there is however, little change in costs due to screening. The estimated increase in costs and follow-up testing is under $100,000.
- **Diet and supplements**: The children who do not die will also require dietary adjustment. Given that the program would save less than one life, the value in the model is averaged between the food and supplements for non-responsive children and supplements for responsive children. The present value of the lifetime cost of diet and supplements is estimated at $125,000 per child. The estimated present value of the increase in cost due to reduced mortality is $12,000.

Net Present Value of Homocystinuria Screening Benefits

The addition of homocystinuria screening in Washington generates modest net benefits of about $1.3 million if and only if Washington purchases MS/MS capacity for another disorder. The Monte Carlo indicates a range of $200,000 to $2.5 million with an existing MS/MS. [72]

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[67] Tolley et al. Indexed to 2001.

[68] Some of the psychological disorders may be treatable; therefore only a 10 year value is used.

[69] Cost of Illness Handbook, Environmental Protection Agency, Office of Pollution Prevention and Toxics, Abt Associates, Cambridge Massachusetts, Table III-5-2.

[70] Based on a 3% discount rate. Note: Homocystinuria does not create sufficient change in outcomes to justify purchase of MS/MS technology. If MS/MS is already purchased for another disorder, then Homocystinuria can be added to the chemical package for a run that is already taking place. Thus the marginal cost is the cost of test chemicals, additional standards and controls, interpretation of test results, reporting and follow up of abnormal results.

[71] Based on the estimated share of costs at the clinical program for Metabolic Disorders at the University of Washington and the estimated level of effort based on the disorder. Homocystinuria is more complicated and difficult to manage than other disorders and the average cost per child was adjusted by a factor of 2.

[72] Insurance agencies on the Newborn Screening Committee asked the DOH to estimate the cost per year of life saved. They indicated that they sometimes use the cost per year of life saved as a means of comparing tests and treatment. The cost per year of life saved is estimated at $45,000 per discounted year. This is below the $50,000, which the insurers indicate is the point at which they begin to evaluate a procedure more closely.

The use of normal chemistry without MS/MS generates negative net benefits.

The fact that screening could reduce IQ losses dominates the model values. The reduction in IQ loss saves $1 million. The model is sensitive to the value of IQ and this contributes to the high standard deviation of the Monte Carlo. If no value were assigned to the IQ shift then the model would not generate net benefits. On the other hand, the IQ damage is compliance driven and infants who never experience a normal diet are more likely to stick with their restricted diet. Thus the magnitude of the benefit is possibly underestimated. Of the other benefits, reduced cost of mortality contributes $500,000, reduced personality disorders contribute $500,000, reduced seizures contribute $100,000, reduced cost of clinical identification contributes $45,000 and other factors have a smaller impact. The reader should note that there may be some double counting in the model since some patients may have overlapping conditions.

Testing of all infants generates the largest cost of the program at a present value of $800,000. The cost of added clinical programs costs $100,000. Finally the attendant medical costs of food or vitamins generate some small costs.

The model is very sensitive to the frequency of the disorder and to the value of IQ. Given the low values, the model is also sensitive to the value of personality disorders, statistical life and seizures. If any two of these were reduced the model might not generate an estimate of net benefits.

Estimating Net Benefits		
Gain		**Expected Values**
Mortality avoided	(0.23)	$ 505,169
Reduced cost of clinical Identification	4.7	$ 45,925
Marfan & osteoporosis	0.00	na
Learning disability	(1.84)	$ 394,547
Mild retardation	0.06	$ (22,028)
Significant Retardation	(0.84)	$ 652,501
Seizures	(0.46)	$ 97,147
Personality Disorders	(1.07)	$ 530,348
Ectopia lentis	(1.01)	$ 2,428
Thrombo-embolic events	(0.17)	$ 9,488
Cost		
Cost of diet	0.11	$ 12,422
Cost of supplements	0.23	$ 817
Testing	0.23	$ 5,707
Cost of Clinical Program	0.23	$ 68,985
Cost of Newborn Screening		$ 800,046
Net		**$ 1,327,548**
Net without mortality		$ 822,379
$/year of life saved		$ 45,323

Cost Benefit Analysis for Maple Syrup Urine Disease

Background

Maple Syrup Urine Disease (MSUD), or branched chain ketoaciduria, is rare. Its frequency depends on the racial mix of the population.[73] Washington expects one in 100,000 infants (0.001%) to be born with MSUD. For Washington this means an average of 8.3 infants will be born with MSUD in a ten-year period. However, the University of Washington received 3 MSUD infants in the last year, and tracks 8 other children under 10 years of age and 3 children between 10 and 20 years of age (the latter 3 have mild MSUD). This living population does not take into account the children who died prior to diagnosis. Unless the last 20 years are unrepresentative, Washington may have a higher than average frequency of this disorder.[74]

MSUD is a serious metabolic disorder caused by the inability of the body to process the branched-chain amino acids (BCAAs).[75] Untreated classic MSUD patients usually die in the first months of life from acute metabolic decompensation and neurologic deterioration. There are several phenotypes of MSUD,[76] however patients diagnosed after 14 days rarely achieve normal intelligence and may have other long-term neurologic damage. Survivors may suffer from nervous system damage, orthopedic problems and organ damage.

In most infants branched-chain amino acids are broken down by branched-chain α-keto dehydrogenase. Infants with MSUD have a deficiency in the activity of this enzyme. Thus there is a buildup of BCAAs, leucine, isoleucine, valine and related branched-chain α-keto acids.

Treatment requires intervention during periods of metabolic decompensation and controlling diet. The nature of the intervention and diet shift depends on the form of MSUD. Early identification and good control of the diet generates an improved IQ and medical outcome for most children.

Benefits of MSUD Screening

Screening would provide diagnosis, for many of these infants, just as the infant first presents with symptoms. Screening would allow an immediate shift in the diet. Screening would reduce mortality and the immediate impacts of metabolic decompensation.

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[73] MSUD has multiple genetic causes in each ethnic group. Thus there are multiple phenotypes for each group. Washington has a higher Philippino population than the US as a whole. Given the rarity of the disorder and the greater rarity of the genetic types, the department therefore used an average frequency for Washington as a whole.

[74] Ron Scott, University of Washington. Mike Glass, DOH, Newborn Screening Program, indicates the estimated frequency used here is well within the statistical boundaries for the data from: National Newborn Screening and Genetic Resource Center, National Newborn Screening Report –1996 (October 2000) – 1997 (May 2001) and – 1998 (December 2001) NNSCRC, Austin TX.

[75] Much of the overview information on the function of MSUD is drawn from D.T. Chuang, V.E. Shih, *Maple Syrup Urine Disease (Branched-Chain Ketoaciduria),* Chapter 87, in The Metabolic & Molecular Bases of Inherited Disease, eds. Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill.

[76] There are classic, intermediate, intermittent and thiamine responsive patients. The relative frequency of the phenotypes is not known for Washington and is not modeled.

- Some infants will not die. Currently in a 10-year period, a statistical mortality of 3.3 children would be expected. With newborn screening the statistical mortality is reduced to 2.3 children.
- Some infants will avoid brain damage. All infants with earlier diagnosis would have significantly reduced damage from the early exposure. Approximately 1 child would shift from having mental retardation to have a normal IQ outcome and/or no seizures.
- Reduced costs of clinical identification and reduced cost of stay for early onset of MSUD symptoms.
- Finally, screening will identify some infants with milder forms of MSUD who may benefit from control of the diet and vitamin supplements.

Costs of MSUD Screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs and negative medical outcomes for children who would otherwise have died:

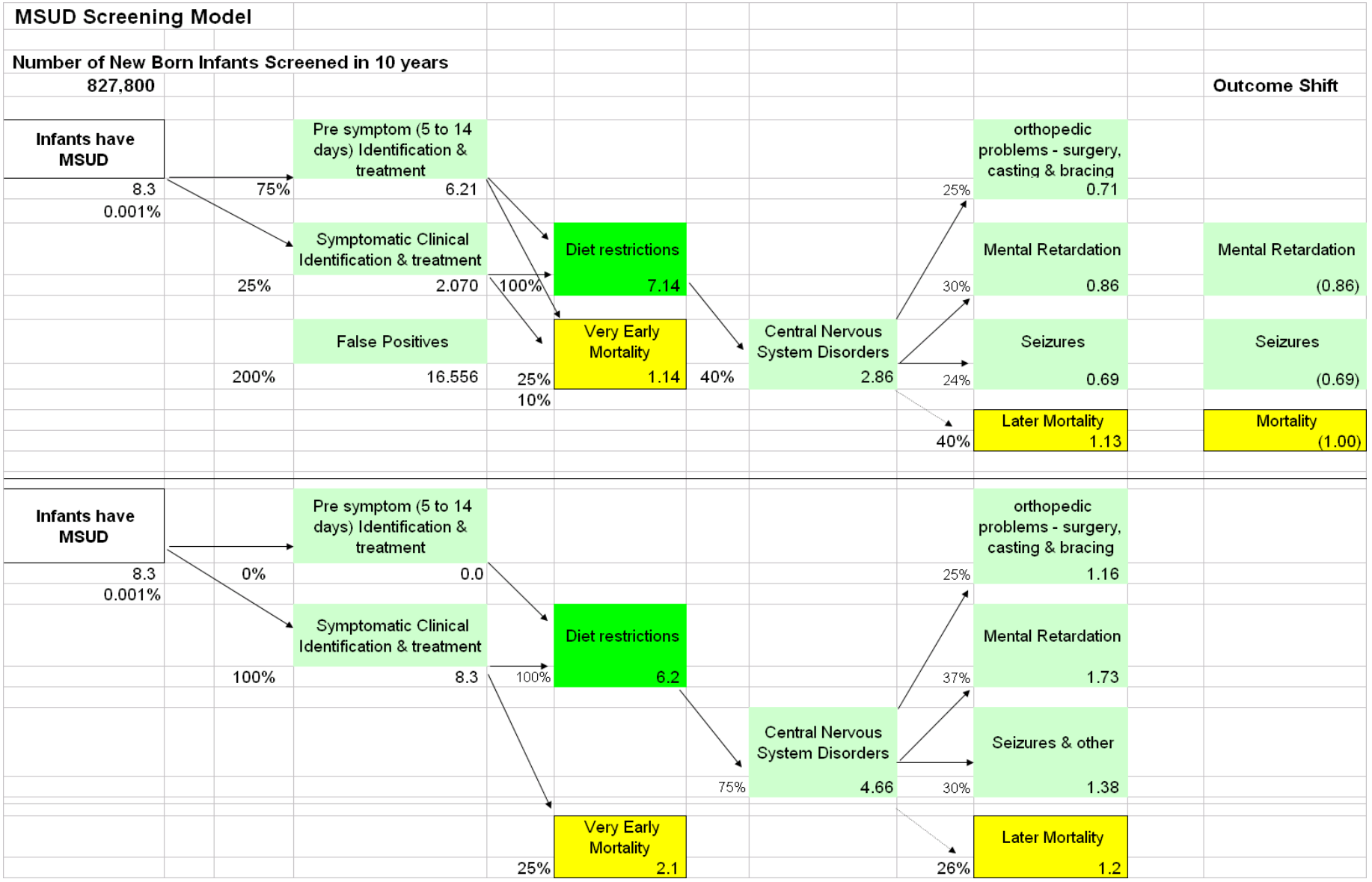
- Screening all newborns: The DOH expects to screen 827,000 newborns at a cost of $1.10 each. The expected present value of this cost for a 10-year program is $800,000.[77]
- Clinical program and monitoring tests: Children with MSUD have to be in a clinical program and be monitored. All children with an initial diagnosis of MSUD will require testing. The clinical program that currently trains families how to select food, explains test results, and intervenes with the child when he or she decides to eat inappropriately. The children who would have died without screening would be expected to cost $20,000 per year and would have a present value of $600,000 in lifetime costs for the children who would have died.
- Food: Special formula is available for infants. Depending on the phenotype various levels of food support may be necessary. This is expected to cost $10 per day.

The MSUD Medical Outcomes Model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the "front end" or left hand side of the model see Figure x). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency**: 1 in 100,000 is the estimated frequency of MSUD. For purposes of the Monte Carlo, this frequency was attached to a Weibull distribution ranging from one in 80,000 to one in 200,000, and a mean of one in 100,000.

[77] Based on a 3% discount rate. The $1.10 per screen is based on an addition to the use of MS/MS for other disorders. The expected cost for the chemical testing is $4 per child.


MSUD Screening Model
Number of New Born Infants Screened in 10 years
827,800
Outcome Shift
Infants have MSUD
8.3
0.001%
75%
Pre symptom (5 to 14 days) Identification & treatment
6.21
25%
Symptomatic Clinical Identification & treatment
2.070
200%
False Positives
16.556
100%
Diet restrictions
7.14
25%
Very Early Mortality
1.14
10%
40%
Central Nervous System Disorders
2.86
25%
orthopedic problems - surgery, casting & bracing
0.71
30%
Mental Retardation
0.86
Mental Retardation
(0.86)
24%
Seizures
0.69
Seizures
(0.69)
40%
Later Mortality
1.13
Mortality
(1.00)
Infants have MSUD
8.3
0.001%
0%
Pre symptom (5 to 14 days) Identification & treatment
0.0
100%
Symptomatic Clinical Identification & treatment
8.3
100%
Diet restrictions
6.2
25%
Very Early Mortality
2.1
75%
Central Nervous System Disorders
4.66
25%
orthopedic problems - surgery, casting & bracing
1.16
37%
Mental Retardation
1.73
30%
Seizures & other
1.38
26%
Later Mortality
1.2

- **Symptomatic Clinical Identification and Treatment:** Symptoms sometimes arrive at 3 or 4 days old, prior to the results from the blood spot. This estimated value is set at 25%.[78]

- **Pre-symptomatic Screening Identification**: DOH expects that 75% of the children would not present early and would be identified prior to the onset of symptoms.

- **False Positives**: Based on past experience with the screening, the program expects to identify approximately 2 children who may have MSUD for each child that has MSUD. These false positives will require an additional test. In the first year, while the program adjusts to the new test, the rate may be higher, because the staff will not want to miss a child.

- **Mortality** occurs at onset or later due to complications. Total mortality is estimated to be reduced by 30%. Very early mortality is estimated at 25% under a program of clinical identification. The later mortality rate for children diagnosed clinically, who have central nervous system damage, is 26%. The later mortality for positively screened children who have central nervous system damage is 40%, however fewer screened children have central nervous system damage and therefore fewer children die.[79] Children, who have been screened are diagnosed more rapidly as the results become available just as the child is presenting with symptoms.[80] The screen is expected to reduce mortality by 1 child every 10 years.

- **IQ outcomes**: IQ loss is associated with central nervous system damage and takes place over the lifespan in the child. Initial damage is substantially reduced by early identification and immediate placement on a diet. Long term damage is reduced or eliminated by good dietary compliance. For clinically diagnosed children 37% of those with central nervous system problems are expected to have IQ loss. For positively screened children, 30% of those with central nervous system problems are expected to have IQ loss.

- **Seizures**: Seizures are associated with central nervous system damage, which takes place over the lifespan in the child. Initial damage is reduced by early identification and immediate placement on a diet. Long-term damage is reduced or eliminated by good dietary compliance. For clinically diagnosed children 30% of those with central nervous system problems are expected to have seizures. For positively screened children, 24% of those with central nervous system problems are expected to have seizures.

- **Orthopedic problems - surgery, casting & bracing**: Orthopedic problems are common. Initial damage is reduced by early identification and immediate placement on a diet. Long-term damage is reduced or eliminated by good dietary compliance. 25% of the children who have central nervous system damage are expected to have orthopedic

[78] Ron Scott, University of Washington.
[79] This apparently inconsistent result is due to the fact that much larger share of the unscreened children die earlier and a smaller share (40% as opposed to 75%) of the screened children have central nervous system damage.
[80] Note: These numbers were back calculated based on mortality given Ron Scott's recent experience with neonates and children.

problems. Here, the nervous system damage is simply used as a linear predictor of damage in other systems.

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is covered in the Galactosemia section above.

- **Mental Retardation:** Neural damage that produces mental retardation is valued at $870,000.[81]

- **Seizure** costs are estimated at $211,000 for a 10-year loss of mobility discounted to begin the 16th year of life. This value has been assigned a normal distribution from $125,000 to $310,000.

- **Orthopedic problems - surgery, casting and bracing:** No value was assigned for this medical problem.

Net Present Value of MSUD Screening Benefits

The addition of MSUD screening in Washington to an existing program using MS/MS generates net benefits of $3.4 million. The Monte Carlo indicates a range of values from $380,000 to $6.8 million with a mean of $3.3 million.

The fact that screening may save 1 life over a 10-year period dominates the model values. The lives saved generate a value of $4 million. The model is sensitive to the assigned value of life and contributes to the high standard deviation of the Monte Carlo. If no value were assigned to life, then the model would not generate net benefits. The other dominant benefit is eliminating one case of mental retardation. This generates a value of $750,000. Other benefits are not nearly as large.[82]

Long-term clinical treatment of children with MSUD generates a cost at a lifetime present value of $600,000. Testing of all infants generates a 10 year present value of cost of $800,000 for the addition of chemicals to an existing battery of tests using tandem mass spectrometry. The attendant medical costs of food and following the children who do not die generates $100,000 in costs.

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[81] Amanda A. Honeycutt, Scott D. Grosse, Laura J. Dunlap, Diana E. Schendel, Hong Chen, Edward Brann, and Ghada al Homsi, Economic Costs of Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment Research in Social Science and Disability, Vol. 3, 207-228, 2003.

[82] Insurance agencies on the Newborn Screening Committee asked the DOH to estimate the cost per year of life saved. They indicated that they sometimes use the cost per year of life saved as a means of comparing tests and treatment. The cost per year of life saved of $20,000 is estimated based on the discounted years.

If tandem mass spectrometry is not available, the cost of the program is $2.9 million. Sensitivity testing using a Monte Carlo indicates the program may generate negative net benefits.

The model is characterized by far greater uncertainty than the other metabolic disorders such as biotinidase deficiency and MCADD. There is no ability to define a realistic estimate of the distribution of the phenotypes for a population the size of Washington's. This limits the ability to define distributions for the medical outcome model. However, if tandem mass spectrometry is available and MSUD is an addition to an existing scan, it is likely that the program would generate net benefits.

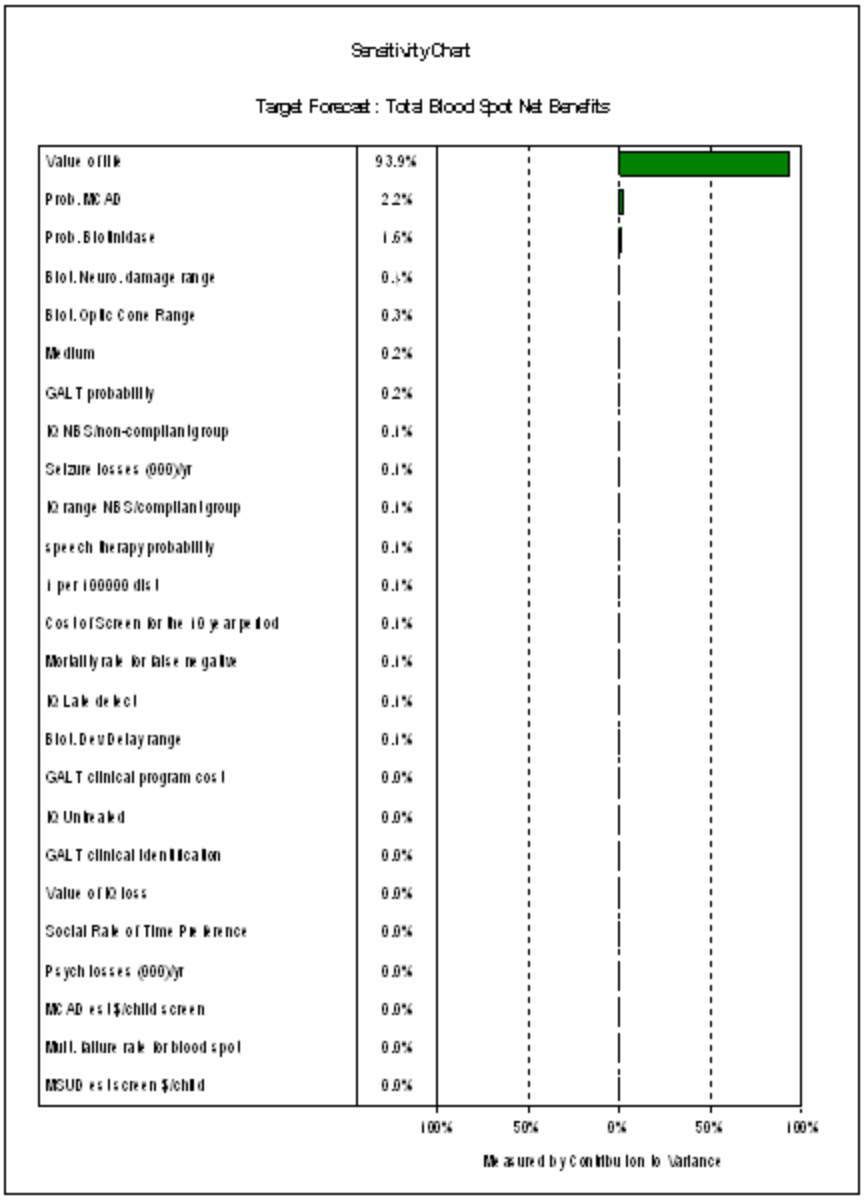
Estimating Net Benefits		
Gain		**Expected Values**
Mortality avoided	(1.00)	$ 4,012,762
Reduced cost of clinical Identification	6.2	$ 137,611
Mental Retardation	(0.9)	$ 754,169
Seizures	(0.69)	$ 93,721
Cost		
Change in cost of food program	(1.00)	$ (110,750)
Clinical Testing		$ (44,779)
Change in Cost of Clinical Program	(1.00)	$ (615,051)
Cost of Newborn Screening		$ (800,046)
Net		**$ 3,427,637**
Net without mortality		$ (585,125)
$/year of life saved		$ 19,840

Appendix 1: Monte Carlo

Crystal Ball Report

Simulation started on 7/30/03 at 9:39:42

Simulation stopped on 7/30/03 at 9:40:04



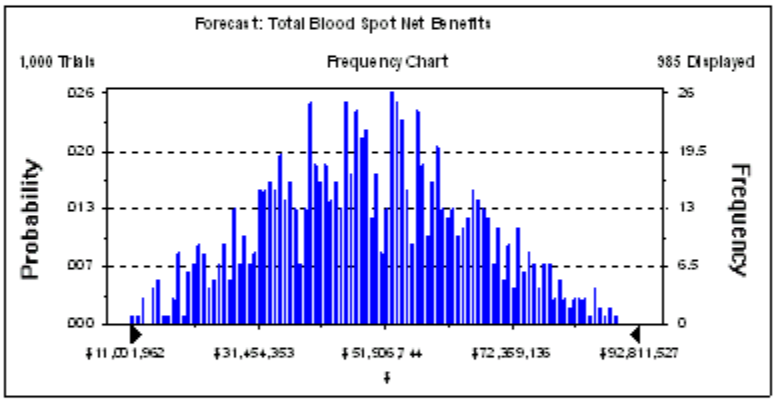
Forecast: Total Blood Spot Net Benefits

[UW program rollupl 7 18 03.xls]Rollup - Cell: C17

Summary:

Display Range is from $11,001,962 to $92,811,527 $
Entire Range is from $10,981,932 to $105,244,782 $
After 1,000 Trials, the Std. Error of the Mean is $540,344

Statistics:	Value
Trials	1000
Mean	$50,130,937
Median	$49,270,776
Mode	—
Standard Deviation	$17,087,180
Variance	3E+14
Skewness	0.23
Kurtosis	2.84
Coeff. of Variability	0.34
Range Minimum	$10,981,932
Range Maximum	$105,244,782
Range Width	$94,262,850
Mean Std. Error	$540,344.06



Forecast: Total Blood Spot Net Benefits (cont'd)

[UW program rollupl 7 18 03.xls]Rollup - Cell: C17

Percentiles:

Percentile	$
0%	$10,981,932
10%	$28,008,883
20%	$34,965,295
30%	$40,318,133
40%	$45,511,373
50%	$49,270,776
60%	$54,022,344
70%	$58,787,037
80%	$64,859,011
90%	$72,359,977
100%	$105,244,782

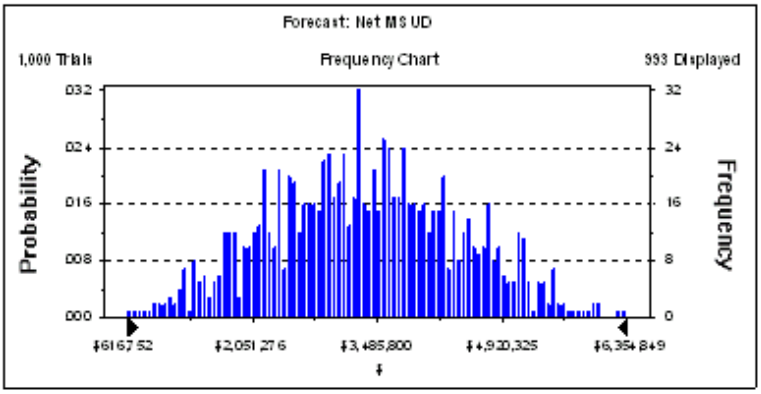
End of Forecast

Forecast: Net MSUD **[MSUD decision model 7 18_03.xls]Values - Cell: D30**

Summary:

Display Range is from $616,752 to $6,354,849 $
Entire Range is from $382,678 to $6,848,902 $
After 1,000 Trials, the Std. Error of the Mean is $35,191

Statistics:	Value
Trials	1000
Mean	$3,356,213
Median	$3,316,135
Mode	—
Standard Deviation	$1,112,843
Variance	1E+12
Skewness	0.12
Kurtosis	2.71
Coeff. of Variability	0.33
Range Minimum	$382,678
Range Maximum	$6,848,902
Range Width	$6,466,223
Mean Std. Error	$35,191.20



[MSUD decision model 7 18_03.xls]Values - Cell: D30

Forecast: Net MSUD (cont'd)

Percentiles:

Percentile	$
0%	$382,678
10%	$1,886,738
20%	$2,358,024
30%	$2,737,540
40%	$3,043,788
50%	$3,316,135
60%	$3,627,930
70%	$3,937,578
80%	$4,305,922
90%	$4,826,428
100%	$6,848,902

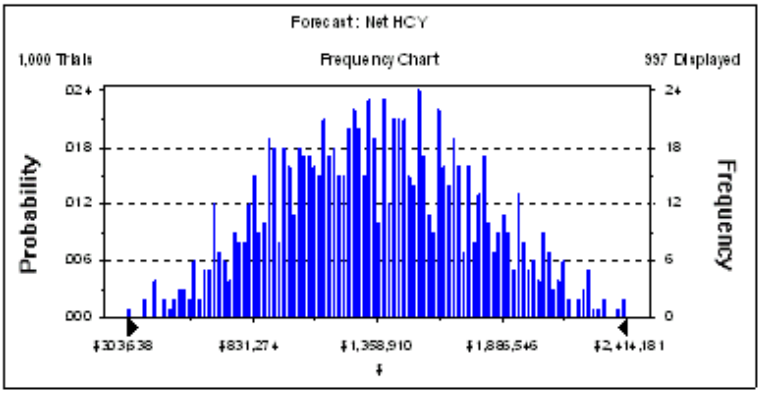
End of Forecast

Forecast: Net HCY **[hcy model 7 18 03 .xls]Values - Cell: D50**

Summary:

Display Range is from $303,638 to $2,414,181 $
Entire Range is from $278,634 to $2,517,227 $
After 1,000 Trials, the Std. Error of the Mean is $13,070

Statistics:	Value
Trials	1000
Mean	$1,352,961
Median	$1,340,433
Mode	—
Standard Deviation	$413,308
Variance	2E+11
Skewness	0.08
Kurtosis	2.49
Coeff. of Variability	0.31
Range Minimum	$278,634
Range Maximum	$2,517,227
Range Width	$2,238,593
Mean Std. Error	$13,069.94



Forecast: Net HCY (cont'd) **[hcy model 7 18 03 .xls]Values - Cell: D50**

Percentiles:

Percentile	$
0%	$278,634
10%	$822,159
20%	$974,316
30%	$1,109,268
40%	$1,234,145
50%	$1,340,433
60%	$1,461,088
70%	$1,582,269
80%	$1,710,819
90%	$1,906,294
100%	$2,517,227

End of Forecast

Forecast: Net Biotinidase

[biotinidase screening decision model 7 18 03.xls]Values - Cell: D38

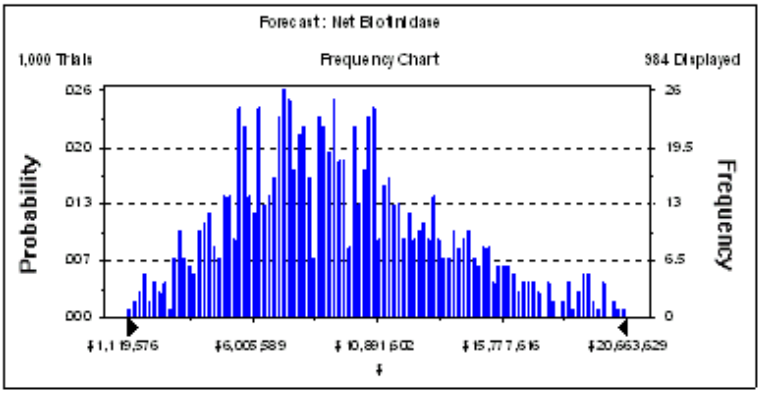
Summary:

Display Range is from $1,119,576 to $20,663,629 $

Entire Range is from $1,119,576 to $29,777,447 $

After 1,000 Trials, the Std. Error of the Mean is $136,622

Statistics:	Value
Trials	1000
Mean	$9,632,092
Median	$9,087,649
Mode	—
Standard Deviation	$4,320,364
Variance	2E+13
Skewness	0.77
Kurtosis	3.80
Coeff. of Variability	0.45
Range Minimum	$1,119,576
Range Maximum	$29,777,447
Range Width	$28,657,871
Mean Std. Error	$136,621.89



Forecast: Net Biotinidase (cont'd)

[biotinidase screening decision model 7 18 03.xls]Values - Cell: D38

Percentiles:

Percentile	$
0%	$1,119,576
10%	$4,607,824
20%	$5,936,130
30%	$7,154,794
40%	$7,986,149
50%	$9,087,649
60%	$10,189,341
70%	$11,339,497
80%	$13,047,127
90%	$15,330,840
100%	$29,777,447

End of Forecast

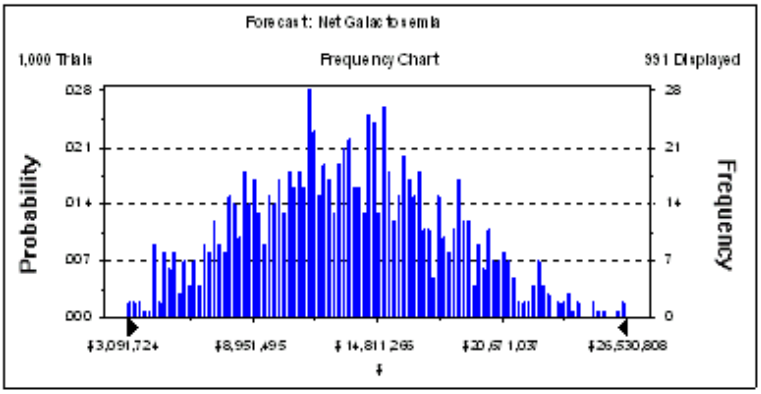
Forecast: Net Galactosemia

[Galactosemia screening decision model 7 18 03.xls]Values - Cell: D40

Summary:

Display Range is from $3,091,724 to $26,530,808 $
Entire Range is from $1,784,927 to $28,245,924 $
After 1,000 Trials, the Std. Error of the Mean is $148,618

Statistics:	Value
Trials	1000
Mean	$13,346,134
Median	$13,307,832
Mode	—
Standard Deviation	$4,699,711
Variance	2E+13
Skewness	0.14
Kurtosis	2.68
Coeff. of Variability	0.35
Range Minimum	$1,784,927
Range Maximum	$28,245,924
Range Width	$26,460,997
Mean Std. Error	$148,617.92



Forecast: Net Galactosemia (cont'd)

[Galactosemia screening decision model 7 18 03.xls]Values - Cell: D40

Percentiles:

Percentile	$
0%	$1,784,927
10%	$7,209,845
20%	$9,118,093
30%	$10,721,979
40%	$11,938,606
50%	$13,307,832
60%	$14,564,798
70%	$15,826,514
80%	$17,352,688
90%	$19,572,490
100%	$28,245,924

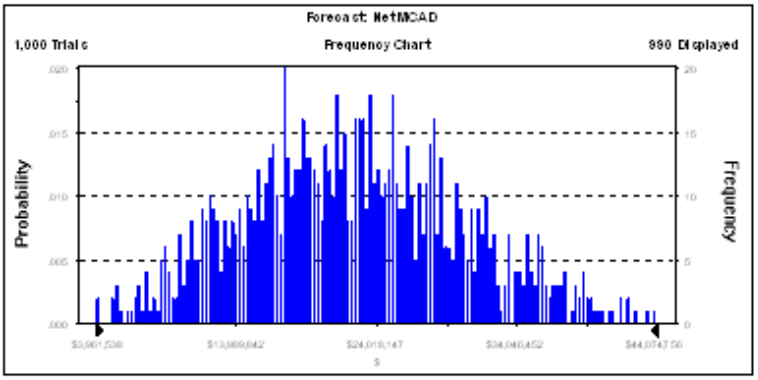
End of Forecast

Forecast: Net MCAD **[MCAD 7 18 03 FINAL.xls]Values - Cell: D58**

Summary:

Display Range is from $3,961,538 to $44,074,756 $
Entire Range is from $3,678,099 to $48,340,132 $
After 1,000 Trials, the Std. Error of the Mean is $254,049

Statistics:	Value
Trials	1000
Mean	$22,443,535
Median	$22,108,323
Mode	—
Standard Deviation	$8,033,749
Variance	6E+13
Skewness	0.29
Kurtosis	2.86
Coeff. of Variability	0.36
Range Minimum	$3,678,099
Range Maximum	$48,340,132
Range Width	$44,662,033
Mean Std. Error	$254,049.46



Forecast: Net MCAD (cont'd) **[MCAD 7 18 03 FINAL.xls]Values - Cell: D58**

Percentiles:

Percentile	$
0%	$3,678,099
10%	$12,031,018
20%	$15,539,168
30%	$17,774,616
40%	$19,877,902
50%	$22,108,323
60%	$24,112,267
70%	$26,357,437
80%	$28,996,649
90%	$33,019,747
100%	$48,340,132

End of Forecast

Assumptions

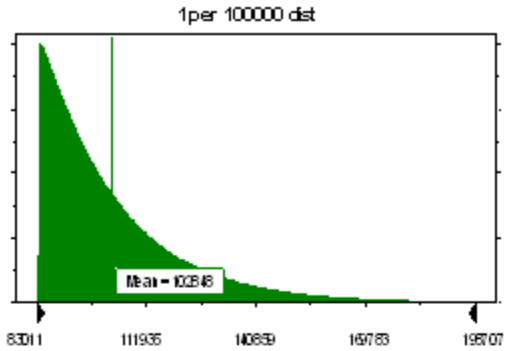
[MSUD decision model 7 18_03.xls]mike's data - Cell: K48

Assumption: 1 per 100000 dist

Weibull distribution with parameters:

Location	83011
Scale	20000
Shape	1.02

Selected range is from 83011 to +Infinity

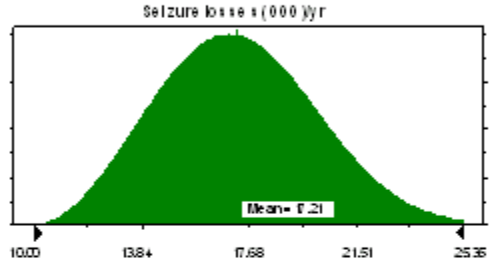


Assumption: Seizure losses (000)/yr **[hcy model 7 18 03 .xls]data - Cell: D194**

Weibull distribution with parameters:

Location	10.00
Scale	8.10
Shape	2.8

Selected range is from 10.00 to +Infinity

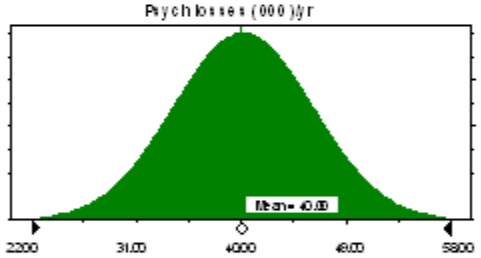


Assumption: Psych losses (000)/yr **[hcy model 7 18 03 .xls]data - Cell: D188**

Normal distribution with parameters:

Mean	40.00
Standard Dev.	6.00

Selected range is from -Infinity to +Infinity



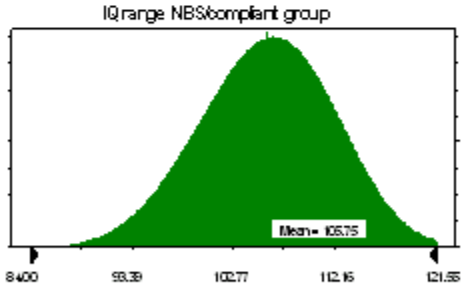
[hcy model 7 18 03 .xls]data - Cell: E249

Assumption: IQ range NBS/compliant group

Weibull distribution with parameters:

Location	84.00
Scale	24.00
Shape	4

Selected range is from -250.41 to +Infinity



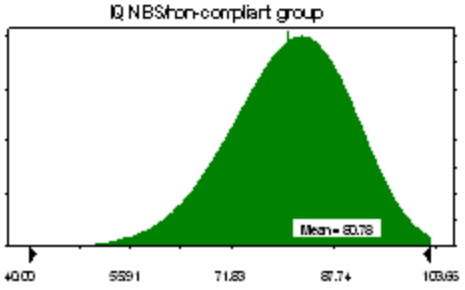
[hcy model 7 18 03 .xls]data - Cell: E251

Assumption: IQ NBS/non-compliant group

Weibull distribution with parameters:

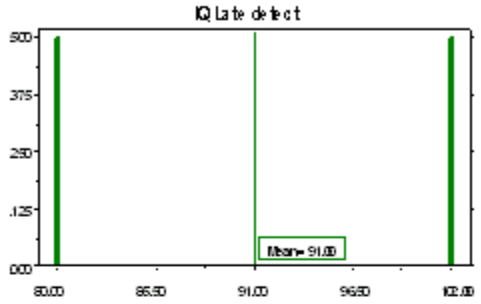
Location	40.00
Scale	44.50
Shape	5

Selected range is from 40.00 to 103.00



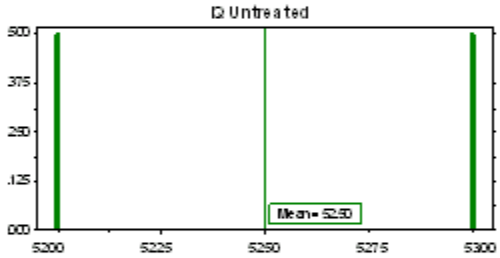
Assumption: IQ Late detect **[hcy model 7 18 03 .xls]data - Cell: E255**

Custom distribution with parameters:		Relative Prob.
Single point	80.00	0.500000
Single point	102.00	0.500000
Total Relative Probability		1.000000



Assumption: IQ Untreated **[hcy model 7 18 03 .xls]data - Cell: E257**

Custom distribution with parameters:		Relative Prob.
Single point	52.00	0.500000
Single point	53.00	0.500000
Total Relative Probability		1.000000

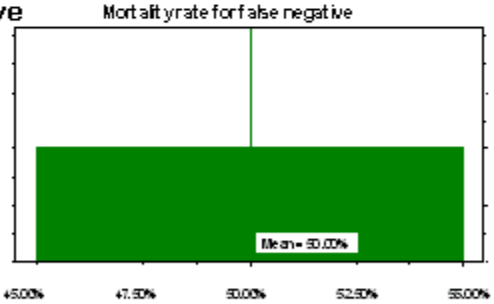


[biotinidase screening decision model 7 18 03.xls]Screen model - Cell: F30

Assumption: Mortality rate for false negative

Uniform distribution with parameters:

Minimum	45.00%
Maximum	55.00%



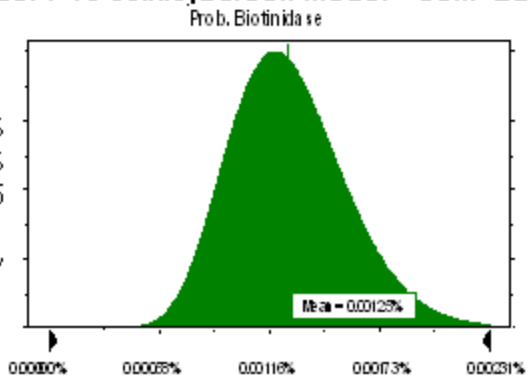
[biotinidase screening decision model 7 18 03.xls]Screen model - Cell: B21

Assumption: Prob. Biotinidase

Gamma distribution with parameters:

Location	0.00000%
Scale	0.00007%
Shape	16.74447665

Selected range is from 0.00000% to +Infinity



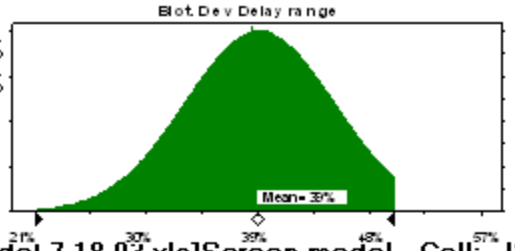
Assumption: Biot. Dev Delay range

[biotinidase screening decision model 7 18 03.xls]Screen model - Cell: J20

Normal distribution with parameters:

Mean	39%
Standard Dev.	6%

Selected range is from 12% to 50%



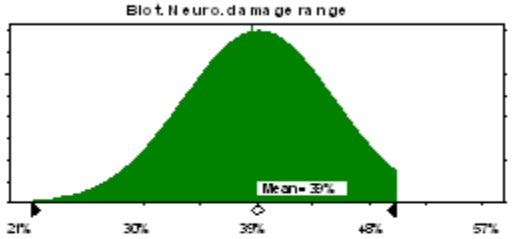
[biotinidase screening decision model 7 18 03.xls]Screen model - Cell: J23

Assumption: Biot. Neuro. damage range

Normal distribution with parameters:

Mean	39%
Standard Dev.	6%

Selected range is from -Infinity to 50%



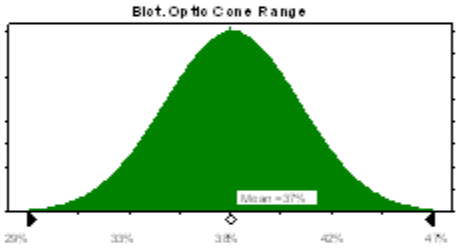
Assumption: Biot. Optic Cone Range

[biotinidase screening decision model 7 18 03.xls]Screen model - Cell: J26

Normal distribution with parameters:

Mean	38%
Standard Dev.	3%

Selected range is from 24% to 49%



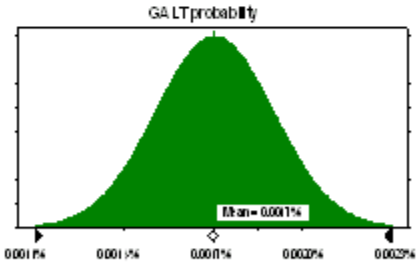
Assumption: GALT probability

[Galactosemia screening decision model 7 18 03.xls]Screen model - Cell: B33

Normal distribution with parameters:

Mean	0.0017%
Standard Dev.	0.0002%

Selected range is from -Infinity to +Infinity

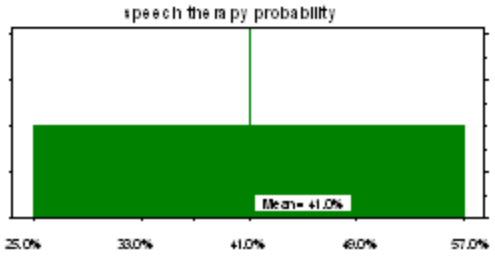


Assumption: speech therapy probability

[Galactosemia screening decision model 7 18 03.xls]Screen model - Cell: M22

Uniform distribution with parameters:

Minimum	25.0%
Maximum	57.0%



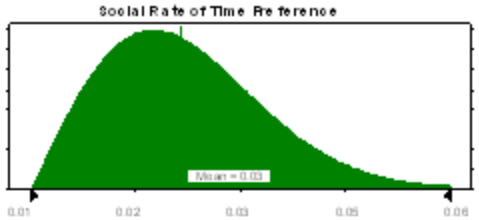
Assumption: Social Rate of Time Preference

[Galactosemia screening decision model 7 18 03.xls]Present value - Cell: A1

Weibull distribution with parameters:

Location	0.01
Scale	0.02
Shape	2

Selected range is from 0.01 to 0.07

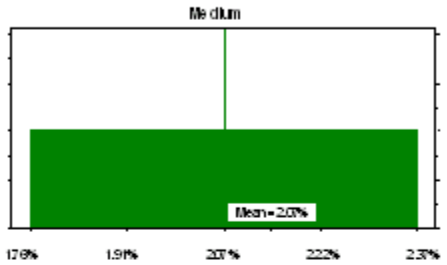


[Galactosemia screening decision model 7 18 03.xls]Value IQ data - Cell: H7

Assumption: Medium

Uniform distribution with parameters:

Minimum	1.76%
Maximum	2.37%



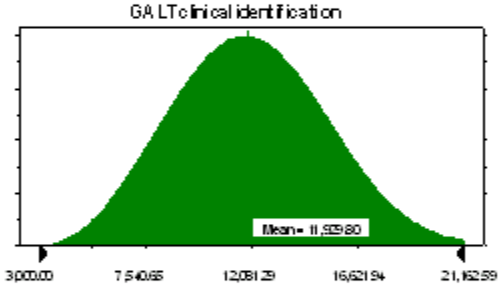
[Galactosemia screening decision model 7 18 03.xls]data - Cell: D59

Assumption: GALT clinical identification

Weibull distribution with parameters:

Location	3,000.00
Scale	10,000.00
Shape	3

Selected range is from 3,000.00 to +Infinity



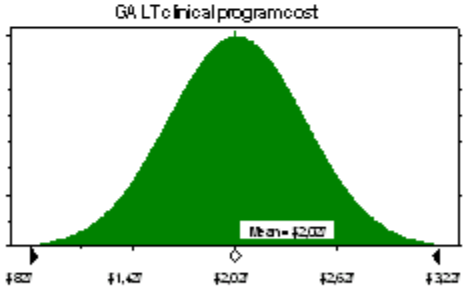
[Galactosemia screening decision model 7 18 03.xls]data - Cell: B62

Assumption: GALT clinical program cost

Normal distribution with parameters:

Mean	$2,027
Standard Dev.	$400

Selected range is from -Infinity to +Infinity



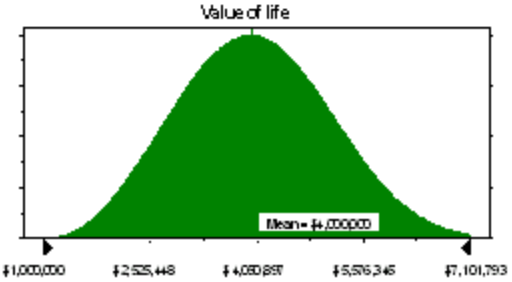
[Galactosemia screening decision model 7 18 03.xls]data - Cell: D14

Assumption: Value of life

Weibull distribution with parameters:

Location	$1,000,000
Scale	$3,359,540
Shape	3

Selected range is from $1,000,000 to +Infinity



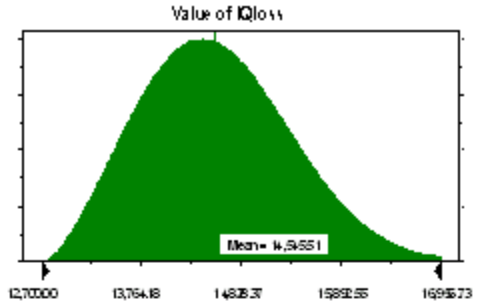
[Galactosemia screening decision model 7 18 03.xls]data - Cell: D21

Assumption: Value of IQ loss

Weibull distribution with parameters:

Location	12,700.00
Scale	2,080.00
Shape	2.5

Selected range is from 12,700.00 to +Infinity

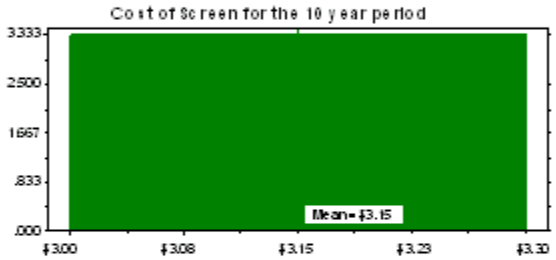


[Galactosemia screening decision model 7 18 03.xls]data - Cell: A38

Assumption: Cost of Screen for the 10 year period

Custom distribution with parameters:

				Relative Prob.
Continuous range	$3.00	to	$3.30	1.000000
Total Relative Probability				1.000000



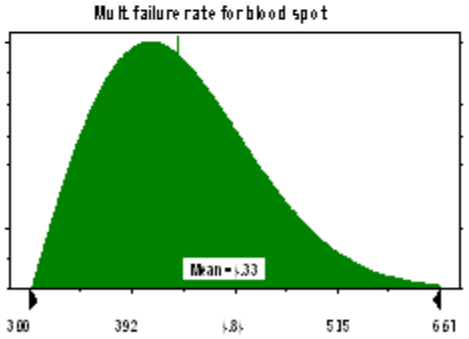
[Galactosemia screening decision model 7 18 03.xls]data - Cell: I38

Assumption: Mult. failure rate for blood spot

Weibull distribution with parameters:

Location	3.00
Scale	1.50
Shape	2

Selected range is from 3.00 to +Infinity

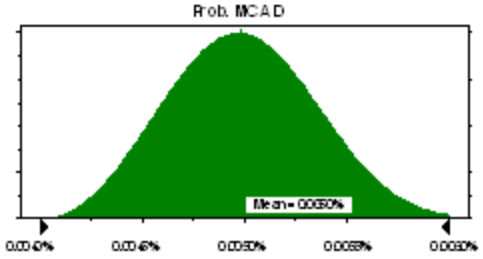


Assumption: Prob. MCAD [MCAD 7 18 03 FINAL.xls]Screen model - Cell: B23

Weibull distribution with parameters:

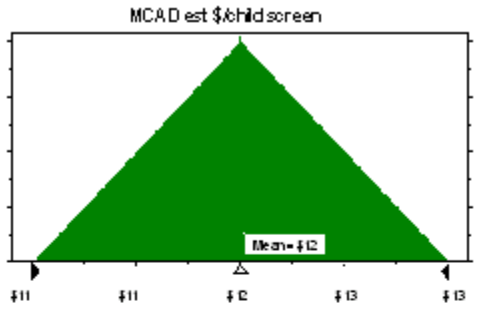
Location	0.0040%
Scale	0.0011%
Shape	3

Selected range is from 0.0040% to +Infinity



[MCAD 7 18 03 FINAL.xls]Values - Cell: D115

Assumption: MCAD est $/child screen



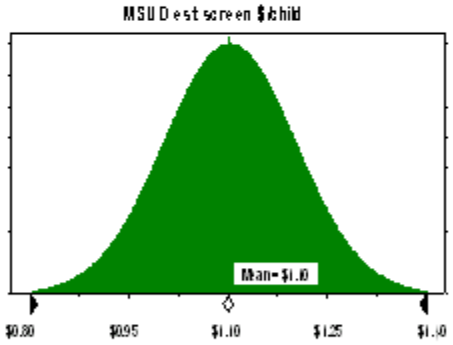
Triangular distribution with parameters:

Minimum	$11
Likeliest	$12
Maximum	$13

Selected range is from $11 to $13

[MSUD decision model 7 18_03.xls]data - Cell: B24

Assumption: MSUD est screen $/child



Normal distribution with parameters:

Mean	$1.10
Standard Dev.	$0.10

Selected range is from -Infinity to +Infinity

End of Assumptions